



Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number:

0 350 948
A2

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 89112955.3

(51) Int. Cl.4: C07D 487/22 , A61K 31/40 ,
A61K 49/00 , // (C07D487/22,
257:00,209:00,209:00,209:00,
209:00)

(22) Date of filing: 14.07.89

(30) Priority: 14.07.88 JP 173835/88
12.06.89 JP 146615/89

(43) Date of publication of application:
17.01.90 Bulletin 90/03

(64) Designated Contracting States:
CH DE FR GB IT LI

(71) Applicant: TOYOHAKKA KOGYO KABUSHIKI
KAISHA
75-1, Hamanaka Satosho-machi
Asakuchi-gun Okayama-ken(JP)

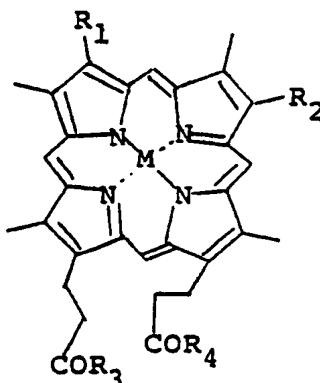
(72) Inventor: SAKATA,Isao
1766-4,Kohirai
Kasaoka-shi,Okayama-ken(JP)

Inventor: NAKAJIMA, Susumu
4-34, Gojyo 4-chome, Midorigaoka
Asahikawa-shi, Hokkaido(JP)
Inventor: Koshimizu, Koichi
856-10, Soenishi-machi, Horenayama
Nara-shi, Nara-ken(JP)
Inventor: Takada, Hiroyuki
2098, Satomi, Satosho-machi
Asakuchi-gun, Okayama-ken(JP)
Inventor: Inui, Hiroshi
2430, Kasaoka, Kasaoka-shi
Okayama-ken(JP)

(74) Representative: Vossius & Partner
Siebertstrasse 4 P.O. Box 86 07 67
D-8000 München 86(DE)

(56) Porphyrin derivatives.

(57) The subject matter of the invention are metallocporphyrin compounds represented by the general formula (I)



EP 0 350 948 A2

wherein

R1 and R2 are each -CH=CH₂, -CH(OR)CH₃ or -CH(O-lower alkylene-OR)CH₃;

R3 and R4 are -OH or a residue obtained by removing a hydrogen atom from a polyfunctional compound;

EP 0 350 948 A2

R is -H, alkyl, alkenyl, perfluoroalkyl, a cyclic compound, or a residue obtained by removing a hydrogen atom from a polyfunctional compound; and

M is a metal.

The compounds of the invention may be used as a therapeutic or diagnostic agent for malignant tumors, as a tumor marker or as an agent for use in the missile therapy of cancers.

Porphyrin Derivatives

The present invention concerns a novel composition having affinity to cancerous tissues and containing as an effective component metalloporphyrin derivative(s) for use as a tumor marker, and for diagnosis and treatment of cancers.

It is well known in the art that porphyrin derivatives selectively accumulate in cancer tissues. However, 5 this selectivity is not necessarily sufficient. Porphyrin derivatives, on the other hand, manifest toxicity when exposed to light, and patients to which these substances have been administered are required to stay in the dark for an extended period of time before the porphyrin derivatives which have accumulated in their normal tissues are completely discharged out of their body.

It has been found that metalloporphyrins obtained by introducing a certain metal into the porphyrin 10 skeletons (JP-A-61-83185) and porphyrin derivatives having a chelate-forming group (JP-B-63-13997) had their photo-toxicity decreased while retaining affinity to cancer. It was also discovered that amino acid bearing porphyrin derivatives having groups which are labelled by iodine and those which have fluorine (JP- 15 A-64-61481) show similar activities.

When the substance of JP-B-63-13997 was labelled with ^{111}In or $^{99\text{m}}\text{Tc}$, and the substance of JP-A-64- 20 61481 with ^{125}I in order to obtain RI imagings of tumor bearing animals, it was found that the excretion rate of these substances from their liver was quite slow and not necessarily complete, suggesting that these substances are not suitable for diagnosing and treating all kinds of cancers of all the sites.

On the other hand, JP-A-62- 5912, 62-5924, 62-5985 and 62-5986 disclose syntheses of various amino 25 acid derivatives of porphyrin, use of monoamino acid derivatives of chlorin in photodiagnosis of cancers using a laser fluorescence endoscopy analyser, and cancer treatment with laser. However, said compounds are not metalloporphyrin derivatives, and were developed solely for diagnosis and therapy with laser irradiation. In its table of efficacies, there are noted side effects such as swelling of the legs and damages to the muscles, thus indicating considerable toxicity of said compounds. Use of a metalloporphyrin derivative in diagnosing and treatment of cancer with laser is reported using protoporphyrin Sn and Mg complexes (JP-A-63-264524). These metalloprotoporphyrin derivatives do not accumulate in cancer tissues selectively.

Paramagnetic metals such as Mn and Fe are used as the contrast medium for magnetic resonance imaging (MRI). Philip et al synthesized Mn-tetraphenyl porphine trisulfonate (Mn-TPPS) for use in MRI (Cancer Research 48, 4604 (1988)). This TPPS derivative demonstrates a potent toxicity and lacks 30 selectivity for cancer tissues, and is therefore not fit for practical use.

Sodium Hg-hematoxylin and protoporphyrin Co complex were developed and officially registered as pharmaceuticals as the porphyrin compounds with anti-tumor effects. However, the former was judged as "without cause to determine its efficacy" in 1960 and the latter in 1982, and their manufacture and sale were respectively suspended.

35 As discussed in the foregoing, selectivity and accumulation of a metalloporphyrin compound obtained by introducing a certain metal into the porphyrin skeleton, of a porphyrin derivative having a chelate forming group, and of a tyrosine bearing porphyrin derivative (group labelled by iodine) are not optimal, and therefore diagnosis and treatment of different cancers on all sites are not always possible. There are currently no porphyrin compounds which have a cell killing effect on their own. A need was therefore felt for 40 a metalloporphyrin derivative which demonstrates potent cancer cell destroying effects on its own, or when used with an external energy such as laser, and a metalloporphyrin derivative useful for MRI which is more potent than the prior substances.

There are porphyrin derivatives which are susceptible to photosensitization and others which are not. The former are inherently defective in that phototoxicity appears, but are useful in therapies such as 45 photodynamic therapy (PDT) and that which uses an external energy. On the other hand, the latter are useful as an agent for diagnosing and treating cancer because they do not induce phototoxicity.

It is the object of the invention to provide novel substances with affinity to cancer cells which show the desired characteristics for use in treatment and diagnosis of cancer, as a tumor marker and in the missile therapy of cancer.

50 This object was solved on the basis of the elucidation of physicochemical characteristics of the cell necrosis effect which porphyrin derivatives demonstrate at photoirradiation. There are two stages of destruction; Mechanism I under which the pigments are excited by light to assume the triple state which directly destroys the cancer cells, and Mechanism II under which the pigments in the triple state further excite oxygen to form the singlet state oxygen (activated oxygen) leading to cell necrosis. In the case of porphyrin derivatives, the Mechanism II is considered prevalent. By measuring the triple state life time (the

fluorescence and phosphorescence life time) which indicates porphyrin's triple state, the length of phosphorescence life time is compared to reveal the intensity of photo-sensitivity. Table 1 shows luminescence properties of various porphyrin derivatives, and indicates that phosphorescence life time is largely affected by the coordination metals of metalloporphyrin derivatives. In other words, phosphorescence life time of metalloporphyrins coordinated with such metals as Zn and Ga is long while that of those coordinated with Mn, Fe, or Cu is very short.

Having considered the above, it was decided to develop metalloporphyrin derivatives with long phosphorescence life time (Ga and Zn complexes) as a drug for treating cancer which uses PDT or an external energy, and those with short phosphorescence life time (Mn, Fe and Cu complexes) as a diagnostic drug for cancer in MRI and RI, and as an antitumor agent on its own. Having conducted further researches on uses of porphyrin derivatives by noting both characteristics (both long and short phosphorescence life time), it was found that if at least one polyfunctional compound was bonded to the side chain of the metalloporphyrin compound, said porphyrin compound with above mentioned properties would be quickly excreted from the normal tissues while maintaining affinity to cancer.

15

Table 1

20	Compounds	Absorbance (nm)	Fluorescence (nm)	Phosphorescence (nm)	Phosphorescence life time (ms)	
					Filter paper	Solution
25	PP-Me	633	635	/	1.8	/
	Mg-PP-Me	590	600	-	-	-
	Mn-PP-Me	570	575	710	20 μ s	20 μ s
	Fe-PP-Me	645	-	-	-	-
	Co-PP-Me	570	-	-	-	-
	Cu-PP-Me	572	-	705	20 μ s	100 μ s
30	Zn-PP-Me	582	588	715	35	/
	Ga-PP-Me	570	575	715	50	200
	In-PP-Me	583	590	730	7.6	14.1
	Sn-PP-Me	583	590	735	7.6	13
35	Me-PPB	670	675	/	1.7	/
	Photofrin-II	620	625	735	9	/

PP: protoporphyrin, PPB: pheophorbide

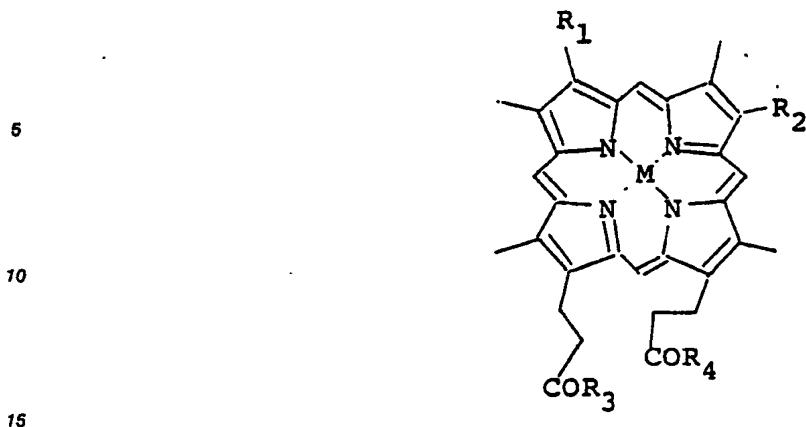
40 The properties of the present invention porphyrin derivatives do not undergo any substantial change even when bonded to other active substances or combined with external energy.

The subject matter of the present invention are metalloporphyrin compounds expressed by the formula (I)

45

50

55



(wherein

R₁ and R₂ are each -CH=CH₂, -CH(OR)CH₃ or -CH(O-lower alkylene-OR)CH₃;

20 R₃ and R₄ are -OH or a residue obtained by removing a hydrogen atom from a polyfunctional compound; R is -H, alkyl, alkenyl, perfluoroalkyl, a cyclic compound, or a residue obtained by removing a hydroxy group from a polyfunctional compound; and M is a metal).

In the above definitions of the symbols, the term "lower alkylene" means alkylene having usually less than 5 carbon atoms, preferably from 1 to 3 carbon atoms (e.g. ethylene, trimethylene, and propylene), while the term "alkyl" means alkyl having usually less than 20 carbon atoms, preferably from 1 to 18 carbon atoms (e.g. methyl, ethyl, n-propyl, hexyl, octyl, decyl, dihydrocitronellyl, undecyl, dodecyl, tetradecyl, and octadecyl), and the term "alkenyl" means alkenyl having less than 20 carbon atoms, preferably from 6 to 16 carbon atoms (e.g. hexenyl, octenyl, geranyl, cytronellyl, and octadecenyl).

30 The term "perfluoroalkyl" means perfluoroalkyl having less than 20 carbon atoms, preferably from 2 to 11 carbon atoms (e.g. hexafluorobutyl, octafluoropentyl, dodecafluoroheptyl, and pentadecafluoroctyl) and the term "cyclic compound" means cyclic compounds having less than 7 membered rings (e.g. cyclohexyl and menthyl).

35 The term "polyfunctional compound" means those having at least 2 functional groups (e.g. -NH₂, -OH, -O-, -SH, -S-, -COOH, and halogen) and, preferably, amino acids (e.g. glycine, cysteine, glutamic acid, alanine, cystine, aspartic acid, asparagine, valine, methionine, glutamine, leucine, phenylalanine, isoleucine, serine, tryptophane, threonine, histidine, lysine, and tyrosine), polyamines (e.g. ethylenediamine, hexamethylenediamine, hydrazine, and tetraethylene pentamine), polyhydric alcohols (e.g. ethylene glycol, methyl cellosolve, ethyl cellosolve, and carbitol), heterocyclic alcohols (e.g. tetrahydrofurfuryl alcohol, tetrahydropyran-2-methanol, and 3-pyridine-methanol), amino alcohols (e.g. monoethanol-amine, 40 dimethylamino ethanol, hydroxyamine, and hydrazino-ethanol), sulfur containing alcohols (e.g. methionol), halogen alcohols (e.g. monobromoethanol and trichloro alcohol), phenethyl alcohol, taurine and hydroxy acetic acid.

45 Some of these substances are optically active, and levo-rotatory compound, dextro-rotatory compound or DL-rotatory compound may be used or that which has converted to DL-rotatory compound during photosynthesis may be used. They may also be used in the form of salt of alkali metal.

The metalloporphyrin compounds (I) according to the present Invention are novel substances, but the compounds per se can be prepared routinely. The process of preparation usually follows the step (a) wherein the porphyrin compound of the formula (I) having R₁ and R₂ is obtained, the step (b) wherein a metal is introduced therein, and the step (c) wherein thus obtained metalloporphyrin compound is bonded at R₃ and R₄ with a residue of a polyfunctional compound (e.g. amino acid). It is not necessarily important to sequentially conduct the reactions in the order of (a), (b) and (c). The order may be varied as (b), (a) and (c), or (a), (c) and (b).

55 The steps (a) and (b) can be performed by a routine method such as that disclosed in J. E. Falk: Porphyrins and Metalloporphyrins (Elsevier, 1975). A metalloporphyrin compound having R₁ and R₂ corresponding to the formula (I) may be prepared according to the methods disclosed in JP-A-61-7279, JP-A-61-83185, and JP-B-63-13997. For the step (a), it is sufficient to introduce R to R₁ and R₂ side chains of the porphyrin compound (I), and the polyfunctional compound may be reacted in respect of its hydroxyl group, or with other functional groups (such as -NH₂ group). If the polyfunctional compound having a

hydroxyl group is to be used, it is preferable to prepare Br derivatives of the porphyrin compound (I) in advance, and to continue reactions with the hydroxyl group of a polyfunctional compound. Other functional groups of the polyfunctional compound therefore may be protected suitably. For the step (b), a metal chloride, acetate, sulfate or nitrate, is usually used. As metals, Mg, Si, Ti, Mn, Fe, Co, Ni, Cu, Zn, Ga, Ge

5 and In are used. The step of metal introduction (b) may be performed before or after the step (a) depending on the need. For instance, the step (b) may be performed first, Br derivatives of metalloporphyrin prepared, and then Br derivative reacted with the functional compound (the step (a)). Instead of artificial synthesis, this compound may be obtained from a natural source such as a plant or an animal.

The thus obtained metalloporphyrin compound is then subjected to the step (c) where it is bonded to 10 the residue of a polyfunctional compound. By reacting a metalloporphyrin compound (I) at least either R₃ or R₄ of which is -OH with a polyfunctional compound (mainly amino acid, polyamine, and amino alcohols), a polyfunctional compound-bearing-metallocporphyrin compound (I) is obtained. This may be performed by a routine method discussed in Izumiya et al: Basis and Test on Peptide Synthesis (Maruzen, 1985) (in Japanese) and by following a method disclosed in JP-A-64-61481. Instead of artificial synthesis, this 15 compound may be obtained from a natural source such as a plant or an animal.

In this case, since the residue of a polyfunctional compound is to be merely introduced into the side chain of the porphyrin compound (I), the polyfunctional compound may be reacted in respect of its amino group, or with other functional groups (such as -OH group). For instance, if a polyfunctional compound having an amino group is to be used, it is preferable to proceed with the reaction between a carboxyl group 20 at R₃ and R₄ side chains of the porphyrin compound (I) and an amino group of a polyfunctional compound. Therefore, it is preferable to convert the former carboxyl group and/or the latter amino group to routine reacting groups, or to suitably protect groups which should not participate in the reaction between the two. In either case, reaction-promoting agents such as a dehydrating agent and a deoxidizer or condensing 25 agents may be used.

25 The process of preparing metallocporphyrin compound (I) is now explained concretely by referring to representative examples. If the polyfunctional compound has an amino group, a metallocporphyrin compound at least either R₃ or R₄ of which is an OH group (JP-A-61-7279, JP-A-61-83185, and JP-B-63-13997) is reacted with the amino group-bearing polyfunctional compound (e.g. amino acid methyl ester) in a solvent using a condensing agent (e.g. dicyclohexylcarbodiimide (DCC) or water soluble carbodiimide (WSC)), and 30 a metallocporphyrin compound (I) having at least one amino group-bearing polyfunctional compound at R₃ and R₄ side chains is obtained. Their concrete examples, and examples of the metallocporphyrin compounds (I) thus produced are discussed below.

- (1) Ga-protoporphynyl monoglycine (hereinafter referred to as Ga-PP-monoGly);
- (2) Ga-protoporphynyl diaspatic acid (hereinafter referred to as Ga-PP-diAsp);
- 35 (3) Ga-protoporphynyl dityrosine (hereinafter referred to as Ga-PP-diTyr);
- (4) 2-[1-(2-hydroxyethoxyethyl]-4-ethenyl-Ga-deuteroporphynyl monoglycine (hereinafter referred to as monoEG-Ga-DP-monoGly);
- (5) 2-[1-(2-hydroxyethoxyethyl]-4-ethenyl-Ga-deuteroporphynyl diglycine (hereinafter referred to as monoEG-Ga-DP-diGly);
- 40 (6) 2-[1-(2-hydroxyethoxyethyl]-4-ethenyl-Ga-deuteroporphynyl dileucine (hereinafter referred to as monoEG-Ga-DP-diLeu);
- (7) 2-[1-(2-hydroxyethoxyethyl]-4-ethenyl-Ga-deuteroporphynyl monoaspartic acid (hereinafter referred to as monoEG-Ga-DP-monoAsp);
- (8) 2-[1-(2-hydroxyethoxyethyl]-4-ethenyl-Ga-deuteroporphynyl diaspatic acid (hereinafter referred 45 to as monoEG-Ga-DP-diAsp);
- (9) 2-[1-(2-hydroxyethoxyethyl]-4-ethenyl-Ga-deuteroporphynyl monophenylalanine (hereinafter referred to as monoEG-Ga-DP-monoPhe);
- (10) 2-[1-(2-hydroxyethoxyethyl]-4-ethenyl-Ga-deuteroporphynyl diphenylalanine (hereinafter referred to as monoEG-Ga-DP-diPhe);
- 50 (11) 2-[1-(2-hydroxyethoxyethyl]-4-ethenyl-Ga-deuteroporphynyl monotyrosine (hereinafter referred to as monoEG-Ga-DP-monoTyr);
- (12) 2-[1-(2-hydroxyethoxyethyl]-4-ethenyl-Ga-deuteroporphynyl dityrosine (hereinafter referred to as monoEG-Ga-DP-diTyr);
- (13) 2,4-bis[1-(2-hydroxyethoxyethyl]-Ga-deuteroporphynyl monoglycine (hereinafter referred to as EG-Ga-DP-monoGly);
- 55 (14) 2,4-bis[1-(2-hydroxyethoxyethyl]-Ga-deuteroporphynyl diglycine (hereinafter referred to as EG-Ga-DP-diGly);
- (15) 2,4-bis[1-(2-hydroxyethoxyethyl]-Ga-deuteroporphynyl monoleucine (hereinafter referred to as

EG-Ga-DP-monoLeu);

(16) 2,4-bis[1-(2-hydroxyethoxyethyl)-Ga-deuteroporphynyl dileucine (hereinafter referred to as EG-Ga-DP-diLeu);

(17) 2,4-bis[1-(2-hydroxyethoxyethyl)-Ga-deuteroporphynyl monoisoleucine (hereinafter referred to as EG-Ga-DP-monolle);

(18) 2,4-bis[1-(2-hydroxyethoxyethyl)-Ga-deuteroporphynyl dilsoleucine (hereinafter referred to as EG-Ga-DP-dlle);

(19) 2,4-bis[1-(2-hydroxyethoxyethyl)-Ga-deuteroporphynyl monoserine (hereinafter referred to as EG-Ga-DP-monoSer);

(20) 2,4-bis[1-(2-hydroxyethoxyethyl)-Ga-deuteroporphynyl monocysteine (hereinafter referred to as EG-Ga-DP-monoCys);

(21) 2,4-bis[1-(2-hydroxyethoxyethyl)-Ga-deuteroporphynyl monomethionine (hereinafter referred to as EG-Ga-DP-monoMet);

(22) 2,4-bis[1-(2-hydroxyethoxyethyl)-Ga-deuteroporphynyl monoaspartic acid (hereinafter referred to as EG-Ga-DP-monoAsp);

(23) 2,4-bis[1-(2-hydroxyethoxyethyl)-Ga-deuteroporphynyl mono[D]aspartic acid (hereinafter referred to as EG-Ga-DP-Mono[D]Asp);

(24) 2,4-bis[1-(2-hydroxyethoxyethyl)-Ga-deuteroporphynyl diaspatic acid (hereinafter referred to as EG-Ga-DP-diAsp);

(25) 2,4-bis[1-(2-hydroxyethoxyethyl)-Ga-deuteroporphynyl monoasparagine (hereinafter referred to as EG-Ga-DP-monoAsn);

(26) 2,4-bis[1-(2-hydroxyethoxyethyl)-Ga-deuteroporphynyl monoglutamic acid (hereinafter referred to as EG-Ga-DP-monoGlu);

(27) 2,4-bis[1-(2-hydroxyethoxyethyl)-Ga-deuteroporphynyl diglutamic acid (hereinafter referred to as EG-Ga-DP-diGlu);

(28) 2,4-bis[1-(2-hydroxyethoxyethyl)-Ga-deuteroporphynyl monolysine (hereinafter referred to as EG-Ga-DP-monoLys);

(29) 2,4-bis[1-(2-hydroxyethoxyethyl)-Ga-deuteroporphynyl monophenylalanine (hereinafter referred to as EG-Ga-DP-monoPhe);

(30) 2,4-bis[1-(2-hydroxyethoxyethyl)-Ga-deuteroporphynyl diphenylalanine (hereinafter referred to as EG-Ga-DP-diPhe);

(31) 2,4-bis[1-(2-hydroxyethoxyethyl)-Ga-deuteroporphynyl monotyrosine (hereinafter referred to as EG-Ga-DP-monoTyr);

(32) 2,4-bis[1-(2-hydroxyethoxyethyl)-Ga-deuteroporphynyl dityrosine (hereinafter referred to as EG-Ga-DP-diTyr);

(33) 2,4-bis[1-(2-hydroxyethoxyethyl)-Ga-deuteroporphynyl glycine-aspartic acid (hereinafter referred to as EG-Ga-DP-Gly*Asp);

(34) 2,4-bis[1-(2-hydroxyethoxyethyl)-Ga-deuteroporphynyl serine-aspartic acid (hereinafter referred to as EG-Ga-DP-Ser*Asp);

(35) 2,4-bis[1-(2-hydroxyethoxyethyl)-Ga-deuteroporphynyl aspartic acid-phenylalanine (hereinafter referred to as EG-Ga-DP-Asp*Phe);

(36) 2,4-bis[1-(2-hydroxyethoxyethyl)-Ga-deuteroporphynyl aspartic acid-tyrosine (hereinafter referred to as EG-Ga-DP-Asp*Tyr);

(37) 2,4-bis[1-(2-methoxyethoxyethyl)-Ga-deuteroporphynyl monoserine (hereinafter referred to as MC-Ga-DP-monoSer);

(38) 2,4-bis[1-(2-methoxyethoxyethyl)-Ga-deuteroporphynyl monoaspartic acid (hereinafter referred to as MC-Ga-DP-monoAsp);

(39) 2,4-bis[1-(2-methoxyethoxyethyl)-Ga-deuteroporphynyl diaspatic acid (hereinafter referred to as MC-Ga-DP-diAsp);

(40) 2,4-bis[1-(2-ethoxyethoxyethyl)-Ga-deuteroporphynyl monoaspartic acid (hereinafter referred to as EC-Ga-DP-monoAsp);

(41) 2,4-bis[1-(2-ethoxyethoxyethyl)-Ga-deuteroporphynyl diaspatic acid (hereinafter referred to as EC-Ga-DP-diAsp);

(42) 2,4-bis(1-methoxyethyl)-Ga-deuteroporphynyl monoserine (hereinafter referred to as C₁-Ga-DP-monoSer);

(43) 2,4-bis(1-methoxyethyl)-Ga-deuteroporphynyl monoaspartic acid (hereinafter referred to as C₁-Ga-DP-monoAsp);

(44) 2,4-bis(1-methoxyethyl)-Ga-deuteroporphynyl diaspatic acid (hereinafter referred to as C₁-Ga-

DP-diAsp);

- (45) 2,4-bis(1-methoxyethyl)-Ga-deuteroporphynyl monotyrosine (hereinafter referred to as C₁-Ga-DP-monoTyr);
- (46) 2,4-bis(1-methoxyethyl)-Ga-deuteroporphynyl dityrosine (hereinafter referred to as C₁-Ga-DP-diTyr);
- (47) 2,4-bis(1-ethoxyethyl)-Ga-deuteroporphynyl monoaspartic acid (hereinafter referred to as C₂-Ga-DP-monoAsp);
- (48) 2,4-bis(1-ethoxyethyl)-Ga-deuteroporphynyl diaspatic acid (hereinafter referred to as C₂-Ga-DP-diAsp);
- (49) 2,4-bis(1-propoxyethyl)-Ga-deuteroporphynyl diaspatic acid (hereinafter referred to as C₃-Ga-DP-diAsp);
- (50) 2,4-bis(1-isopropoxyethyl)-Ga-deuteroporphynyl diaspatic acid (hereinafter referred to as C_{3(iso)}-Ga-DP-diAsp);
- (51) 2,4-bis(1-butoxyethyl)-Ga-deuteroporphynyl diaspatic acid (hereinafter referred to as C₄-Ga-DP-diAsp);
- (52) 2,4-bis(1-pentyloxyethyl)-Ga-deuteroporphynyl diserine (hereinafter referred to as C₅-Ga-DP-diSer);
- (53) 2,4-bis(1-pentyloxyethyl)-Ga-deuteroporphynyl diaspatic acid (hereinafter referred to as C₅-Ga-DP-diAsp);
- (54) 2,4-bis(1-hexyloxyethyl)-Ga-deuteroporphynyl diaspatic acid (hereinafter referred to as C₆-Ga-DP-diAsp);
- (55) 2,4-bis(1-heptyloxyethyl)-Ga-deuteroporphynyl diaspatic acid (hereinafter referred to as C₇-Ga-DP-diAsp);
- (56) 2,4-bis(1-octyloxyethyl)-Ga-deuteroporphynyl diglycine (hereinafter referred to as C₈-Ga-DP-diGly);
- (57) 2,4-bis(1-octyloxyethyl)-Ga-deuteroporphynyl diserine (hereinafter referred to as C₈-Ga-DP-diSer);
- (58) 2,4-bis(1-octyloxyethyl)-Ga-deuteroporphynyl diaspatic acid (hereinafter referred to as C₈-Ga-DP-diAsp);
- (59) 2,4-bis(1-octyloxyethyl)-Ga-deuteroporphynyl dityrosine (hereinafter referred to as C₈-Ga-DP-diTyr);
- (60) 2-(1-octyloxyethyl)-4-ethenyl-Ga-deuteroporphynyl diglycine (hereinafter referred to as C_{8(mono)}-Ga-DP-diGly);
- (61) 2-(1-octyloxyethyl)-4-ethenyl-Ga-deuteroporphynyl diserine (hereinafter referred to as C_{8(mono)}-Ga-DP-diSer);
- (62) 2-(1-octyloxyethyl)-4-ethenyl-Ga-deuteroporphynyl diaspatic acid (hereinafter referred to as C_{8(mono)}-Ga-DP-diAsp);
- (63) 2-(1-octyloxyethyl)-4-ethenyl-Ga-deuteroporphynyl dityrosine (hereinafter referred to as C_{8(mono)}-Ga-DP-diTyr);
- (64) 2,4-bis(1-phenethyloxyethyl)-Ga-deuteroporphyrin (hereinafter referred to as C_{8(Phenethyl)}-Ga-DP);
- (65) 2,4-bis(1-phenethyloxyethyl)-Ga-deuteroporphynyl diaspatic acid (hereinafter referred to as C_{8(Phenethyl)}-Ga-DP-diAsp);
- (66) 2,4-bis(1-nonyloxyethyl)-Ga-deuteroporphynyl diaspatic acid (hereinafter referred to as C₉-Ga-DP-diAsp);
- (67) 2,4-bis(1-decyloxyethyl)-Ga-deuteroporphynyl diserine (hereinafter referred to as C₁₀-Ga-DP-diSer);
- (68) 2,4-bis(1-decyloxyethyl)-Ga-deuteroporphynyl diaspatic acid (hereinafter referred to as C₁₀-Ga-DP-diAsp);
- (69) 2,4-bis(1-geranyloxyethyl)-Ga-deuteroporphyrin (hereinafter referred to as C_{10(Gera)}-Ga-DP);
- (70) 2,4-bis(1-geranyloxyethyl)-Ga-deuteroporphynyl diaspatic acid (hereinafter referred to as C_{10(Gera)}-Ga-DP-diAsp);
- (71) 2,4-bis(1-citronellyloxyethyl)-Ga-deuteroporphyrin (hereinafter referred to as C_{10(Citro)}-Ga-DP);
- (72) 2,4-bis(1-citronellyloxyethyl)-Ga-deuteroporphynyl diaspatic acid (hereinafter referred to as C_{10(Citro)}-Ga-DP-diAsp);
- (73) 2,4-bis(1-dihydrocitronellyloxyethyl)-Ga-deuteroporphyrin (hereinafter referred to as C_{10(H₂Citro)}-Ga-DP);
- (74) 2,4-bis(1-dihydrocitronellyloxyethyl)-Ga-deuteroporphynyl diaspatic acid (hereinafter referred to as C_{10(H₂Citro)}-Ga-DP-diAsp);

(75) 2,4-bis(1-undecyloxyethyl)-Ga-deuteroporphynyl diaspatic acid (hereinafter referred to as C₁₁-Ga-DP-diAsp);
 (76) 2,4-bis(1-dodecyloxyethyl)-Ga-deuteroporphynyl diglycine (hereinafter referred to as C₁₂-Ga-DP-diGly);
 5 (77) 2,4-bis(1-dodecyloxyethyl)-Ga-deuteroporphynyl diaspatic acid (hereinafter referred to as C₁₂-Ga-DP-diAsp);
 (78) 2,4-bis(1-dodecyloxyethyl)-Ga-deuteroporphynyl diglutamic acid (hereinafter referred to as C₁₂-Ga-DP-diglu);
 (79) 2,4-bis(1-tetrahydrofuryloxyethyl)-Ga-deuteroporphyrin (hereinafter referred to as H₄Fran-Ga-DP);
 10 (80) 2,4-bis(1-tetrahydrofuryloxyethyl)-Ga-deuteroporphynyl diaspatic acid (hereinafter referred to as H₄Fran-Ga-DP-diAsp);
 (81) 2,4-bis[1-(tetrahydro-2-pyranmethyloxy)ethyl]-Ga-deuteroporphyrin (hereinafter referred to as H₄Pyran-Ga-DP);
 15 (82) 2,4-bis[1-(tetrahydro-2-pyranmethyloxy)ethyl]-Ga-deuteroporphynyl diaspatic acid (hereinafter referred to as H₄Pyran-Ga-DP-diAsp);
 (83) 2,4-bis(1-nicotynyloxyethyl)-Ga-deuteroporphyrin (hereinafter referred to as Nct-Ga-DP);
 (84) 2,4-bis(1-nicotynyloxyethyl)-Ga-deuteroporphynyl diaspatic acid (hereinafter referred to as Nct-Ga-DP-diAsp);
 20 (85) 2,4-bis(1-octafluoropentyloxyethyl)-Ga-deuteroporphynyl diglycine (hereinafter referred to as C₈(F₁₈)-Ga-DP-diAsp);
 (86) 2,4-bis(1-octafluoropentyloxyethyl)-Ga-deuteroporphynyl diaspatic acid (hereinafter referred to as C₈(F₁₈)-Ga-DP-diAsp);
 (87) Mg-protoporphynyl diaspatic acid (hereinafter referred to as Mg-PP-diAsp);
 25 (88) Mg-protoporphynyl dityrosine (hereinafter referred to as Mg-PP-diTyr);
 (89) 2,4-bis[1-(2-hydroxyethyloxy)ethyl]-Mg-deuteroporphyrin (hereinafter referred to as EG-Mg-DP);
 (90) 2,4-bis[1-(2-hydroxyethyloxy)ethyl]-Mg-deuteroporphynyl dityrosine (hereinafter referred to as EG-Mg-DP-diTyr);
 (91) 2,4-bis(1-hexyloxyethyl)-Mg-deuteroporphynyl diaspatic acid (hereinafter referred to as C₆-Mg-DP-diAsp);
 30 (92) 2,4-bis(1-octyloxyethyl)-Mg-deuteroporphynyl diaspatic acid (hereinafter referred to as C₈-Mg-DP-diAsp);
 (93) 2,4-bis(1-decyloxyethyl)-Mg-deuteroporphynyl diaspatic acid (hereinafter referred to as C₁₀-Mg-DP-diAsp);
 35 (94) 2,4-bis(1-decyloxyethyl)-Mg-deuteroporphynyl diaspatic acid (hereinafter referred to as C₁₂-Mg-DP-diAsp);
 (95) Mn-protoporphynyl monotyrosine (hereinafter referred to as Mn-PP-monoTyr);
 (96) Mn-protoporphynyl dityrosine (hereinafter referred to as Mn-PP-diTyr);
 (97) 2-[1-(2-hydroxyethyloxy)ethyl]-4-ethenyl-Mn-deuteroporphyrin (hereinafter referred to as monoEG-Mn-DP);
 40 (98) 2-[1-(2-hydroxyethyloxy)ethyl]-4-ethenyl-Mn-deuteroporphynyl monoglycine (hereinafter referred to as monoEG-Mn-DP-monoGly);
 (99) 2-[1-(2-hydroxyethyloxy)ethyl]-4-ethenyl-Mn-deuteroporphynyl diglycine (hereinafter referred to as monoEG-Mn-DP-diGly);
 (100) 2-[1-(2-hydroxyethyloxy)ethyl]-4-ethenyl-Mn-deuteroporphynyl diaspatic acid (hereinafter referred to as monoEG-Mn-DP-diAsp);
 45 (101) 2-[1-(2-hydroxyethyloxy)ethyl]-4-ethenyl-Mn-deuteroporphynyl diphenylalanine (hereinafter referred to as monoEG-Mn-DP-diPhe);
 (102) 2-[1-(2-hydroxyethyloxy)ethyl]-4-ethenyl-Mn-deuteroporphynyl dityrosine (hereinafter referred to as monoEG-Mn-DP-diTyr);
 50 (103) 2,4-bis[1-(2-hydroxyethyloxy)ethyl]-Mn-deuteroporphyrin (hereinafter referred to as EG-Mn-DP);
 (104) 2,4-bis[1-(2-hydroxyethyloxy)ethyl]-Mn-deuteroporphynyl monoglycine (hereinafter referred to as EG-Mn-DP-monoGly);
 (105) 2,4-bis[1-(2-hydroxyethyloxy)ethyl]-Mn-deuteroporphynyl diglycine (hereinafter referred to as EG-Mn-DP-diGly);
 55 (106) 2,4-bis[1-(2-hydroxyethyloxy)ethyl]-Mn-deuteroporphynyl monoserine (hereinafter referred to as EG-Mn-DP-monoSer);
 (107) 2,4-bis[1-(2-hydroxyethyloxy)ethyl]-Mn-deuteroporphynyl diserine (hereinafter referred to as

EG-Mn-DP-diSer);

- (108) 2,4-bis[1-(2-hydroxyethoxyethyl)-Mn-deuteroporphynyl] monoaspartic acid (hereinafter referred to as EG-Mn-DP-monoAsp);
- (109) 2,4-bis[1-(2-hydroxyethoxyethyl)-Mn-deuteroporphynyl] diaspatic acid (hereinafter referred to as EG-Mn-DP-diAsp);
- (110) 2,4-bis[1-(2-hydroxyethoxyethyl)-Mn-deuteroporphynyl] monophenylalanine (hereinafter referred to as EG-Mn-DP-monoPhe);
- (111) 2,4-bis[1-(2-hydroxyethoxyethyl)-Mn-deuteroporphynyl] diphenylalanine (hereinafter referred to as EG-Mn-DP-diPhe);
- (112) 2,4-bis[1-(2-hydroxyethoxyethyl)-Mn-deuteroporphynyl] monotyrosine (hereinafter referred to as EG-Mn-DP-monoTyr);
- (113) 2,4-bis[1-(2-hydroxyethoxyethyl)-Mn-deuteroporphynyl] dityrosine (hereinafter referred to as EG-Mn-DP-diTyr);
- (114) 2,4-bis(1-pentyloxyethyl)-Mn-deuteroporphynyl diaspatic acid (hereinafter referred to as C₅-Mn-DP-diAsp);
- (115) 2,4-bis(1-octyloxyethyl)-Mn-deuteroporphynyl diglycine (hereinafter referred to as C₈-Mn-DP-diGly);
- (116) 2,4-bis(1-octyloxyethyl)-Mn-deuteroporphynyl diaspatic acid (hereinafter referred to as C₈-Mn-DP-diAsp);
- (117) 2,4-bis(1-decyloxyethyl)-Mn-deuteroporphynyl diglycine (hereinafter referred to as C₁₀-Mn-DP-diGly);
- (118) 2,4-bis(1-decyloxyethyl)-Mn-deuteroporphynyl dialanine (hereinafter referred to as C₁₀-Mn-DP-diAla);
- (119) 2,4-bis(1-decyloxyethyl)-Mn-deuteroporphynyl dileucine (hereinafter referred to as C₁₀-Mn-DP-diLeu);
- (120) 2,4-bis(1-decyloxyethyl)-Mn-deuteroporphynyl serine (hereinafter referred to as C₁₀-Mn-DP-diSer);
- (121) 2,4-bis(1-decyloxyethyl)-Mn-deuteroporphynyl dicysteine (hereinafter referred to as C₁₀-Mn-DP-diCys);
- (122) 2,4-bis(1-decyloxyethyl)-Mn-deuteroporphynyl diaspatic acid (hereinafter referred to as C₁₀-Mn-DP-diAsp);
- (123) 2,4-bis(1-decyloxyethyl)-Mn-deuteroporphynyl di[D]aspartic acid (hereinafter referred to as C₁₀-Mn-DP-di[D]Asp);
- (124) 2,4-bis(1-decyloxyethyl)-Mn-deuteroporphynyl diglutamic acid (hereinafter referred to as C₁₀-Mn-DP-diGlu);
- (125) 2,4-bis(1-decyloxyethyl)-Mn-deuteroporphynyl diphenylalanine (hereinafter referred to as C₁₀-Mn-DP-diPhe);
- (126) 2,4-bis(1-decyloxyethyl)-Mn-deuteroporphynyl diglycidiaspartic acid (hereinafter referred to as C₁₀-Mn-DP-diGly-diAsp);
- (127) 2,4-bis(1-decyloxyethyl)-Mn-deuteroporphynyl dileucylidiaspartic acid (hereinafter referred to as C₁₀-Mn-DP-diLeu-diAsp);
- (128) 2,4-bis(1-decyloxyethyl)-Mn-deuteroporphynyl diphenylalanylidiaspartic acid (hereinafter referred to as C₁₀-Mn-DP-diPhe-diAsp);
- (129) 2-(1-decyloxyethyl)-4-ethenyl-Mn-deuteroporphynyl dileucine (hereinafter referred to as C₁₀-mono-Mn-DP-diLeu);
- (130) 2-(1-decyloxyethyl)-4-ethenyl-Mn-deuteroporphynyl diglutamic acid (hereinafter referred to as C₁₀(mono)-Mn-DP-diGlu);
- (131) 2,4-bis(1-geranyloxyethyl)-Mn-deuteroporphyrin (hereinafter referred to as C_{10(Gera)}-Mn-DP);
- (132) 2,4-bis(1-geranyloxyethyl)-Mn-deuteroporphynyl diaspatic acid (hereinafter referred to as C_{10(Gera)}-Mn-DP-diAsp);
- (133) 2,4-bis(1-citronellyloxyethyl)-Mn-deuteroporphyrin (hereinafter referred to as C_{10(Citro)}-Mn-DP);
- (134) 2,4-bis(1-citronellyloxyethyl)-Mn-deuteroporphynyl monoaspartic acid (hereinafter referred to as C_{10(Citro)}-Mn-DP-monoAsp);
- (135) 2,4-bis(1-citronellyloxyethyl)-Mn-deuteroporphynyl diaspatic acid (hereinafter referred to as C_{10(Citro)}-Mn-DP-diAsp);
- (136) 2,4-bis(1-dihydrocitronellyloxyethyl)-Mn-deuteroporphyrin (hereinafter referred to as C_{10(H₂Citro)}-Mn-DP);
- (137) 2,4-bis(1-dihydrocitronellyloxyethyl)-Mn-deuteroporphynyl diaspatic acid (hereinafter referred to as

as C_{10(H₂Citro)}-Mn-DP-diAsp);

(138) 2-(1-dihydrocitronellyloxyethyl)-4-ethenyl-Mn-deuteroporphynyl diaspatic acid (hereinafter referred to as C_{10(H₂Citro,mono)}-Mn-DP-diAsp);

(139) 2,4-bis(1-menthyloxyethyl)-Mn-deuteroporphyrin (hereinafter referred to as C_{10(Menthyl)}-Mn-DP);

(140) 2,4-bis(1-menthyloxyethyl)-Mn-deuteroporphynyl diaspatic acid (hereinafter referred to as C_{10(Menthyl)}-Mn-DP-diAsp);

(141) 2,4-bis(1-undecyloxyethyl)-Mn-deuteroporphynyl diaspatic acid (hereinafter referred to as C_{11-Mn-DP-diAsp});

(142) 2,4-bis(1-dodecyloxyethyl)-Mn-deuteroporphynyl diglycine (hereinafter referred to as C_{12-Mn-DP-diGly});

(143) 2,4-bis(1-dodecyloxyethyl)-Mn-deuteroporphynyl diaspatic acid (hereinafter referred to as C_{12-Mn-DP-diAsp});

(144) 2,4-bis(1-dodecyloxyethyl)-Mn-deuteroporphynyl diglutamic acid (hereinafter referred to as C_{12-Mn-DP-diGlu});

(145) 2,4-bis(1-dodecyloxyethyl)-Mn-deuteroporphynyl diasparyltetraglycine (hereinafter referred to as C_{12-Mn-DP-diAsp-tetraGly});

(146) 2,4-bis(1-dodecyloxyethyl)-Mn-deuteroporphynyl diasparyltetraaspartic acid (hereinafter referred to as C_{12-Mn-DP-diAsp-tetraAsp});

(147) 2-(1-dodecyloxyethyl)-4-ethenyl-Mn-deuteroporphynyl diaspatic acid (hereinafter referred to as C_{12(mono)-Mn-DP-diAsp});

(148) 2,4-bis(1-tridecyloxyethyl)-Mn-deuteroporphynyl diaspatic acid (hereinafter referred to as C_{13-Mn-DP-diAsp});

(149) 2,4-bis(1-tetradecyloxyethyl)-Mn-deuteroporphynyl diaspatic acid (hereinafter referred to as C_{14-Mn-DP-diAsp});

(150) 2,4-bis(1-tetradecyloxyethyl)-Mn-deuteroporphynyl diasparyltetraaspartic acid (hereinafter referred to as C_{14-Mn-DP-diAsp-tetraAsp});

(151) 2,4-bis(1-farnesyloxyethyl)-Mn-deuteroporphyrin (hereinafter referred to as C_{15(Farnesyl)-Mn-DP});

(152) 2,4-bis(1-farnesyloxyethyl)-Mn-deuteroporphynyl diaspatic acid (hereinafter referred to as C_{15(Farnesyl)-Mn-DP-diAsp});

(153) 2,4-bis(1-hexadecyloxyethyl)-Mn-deuteroporphynyl diaspatic acid (hereinafter referred to as C_{16-Mn-DP-diAsp});

(154) 2,4-bis(1-octadecyloxyethyl)-Mn-deuteroporphynyl diasparyltetraaspartic acid (hereinafter referred to as C_{18-Mn-DP-diAsp-tetraAsp});

(155) 2,4-bis(1-octadecyloxyethyl)-Mn-deuteroporphyrin (hereinafter referred to as C_{18(Oleyl)-Mn-DP});

(156) 2,4-bis(1-octadecyloxyethyl)-Mn-deuteroporphynyl diaspatic acid (hereinafter referred to as C_{18(Oleyl)-Mn-DP-diAsp});

(157) 2,4-bis(1-octadecyloxyethyl)-Mn-deuteroporphynyl diasparyltetraaspartic acid (hereinafter referred to as C_{18(Oleyl)-Mn-DP-diAsp-tetraAsp});

(158) 2,4-bis(1-phytyloxyethyl)-Mn-deuteroporphyrin (hereinafter referred to as C_{20(Phytyl)-Mn-DP});

(159) 2,4-bis(1-tetrahydrofurfuryloxyethyl)-Mn-deuteroporphyrin (hereinafter referred to as H₄Fran-Mn-DP);

(160) 2,4-bis(1-tetrahydrofurfuryloxyethyl)-Mn-deuteroporphynyl diaspatic acid (hereinafter referred to as H₄Fran-Mn-DP-diAsp);

(161) 2,4-bis[1-(tetrahydro-2-pyranmethyloxy)ethyl]-Mn-deuteroporphyrin (hereinafter referred to as H₄Pyran-Mn-DP);

(162) 2,4-bis[1-(tetrahydro-2-pyranmethyloxy)ethyl]-Mn-deuteroporphynyl diaspatic acid (hereinafter referred to as H₄Pyran-Mn-DP-diAsp);

(163) 2,4-bis(1-nicotynyloxyethyl)-Mn-deuteroporphyrin (hereinafter referred to as Nct-Mn-DP);

(164) 2,4-bis(1-nicotynyloxyethyl)-Mn-deuteroporphynyl diaspatic acid (hereinafter referred to as Nct-Mn-DP-diAsp);

(165) 2,4-bis[1-(2-methylthiopropoxyethyl)-Mn-deuteroporphyrin (hereinafter referred to as Msp-Mn-DP);

(166) 2,4-bis[1-(2-methylthiopropoxyethyl)-Mn-deuteroporphynyl diaspatic acid (hereinafter referred to as Msp-Mn-DP-diAsp);

(167) 2,4-bis(1-octafluoropentyloxyethyl)-Mn-deuteroporphyrin (hereinafter referred to as C_{5(F18)-Mn-DP});

(168) 2,4-bis(1-octafluoropentyloxyethyl)-Mn-deuteroporphynyl diglycine (hereinafter referred to as C_{5(F18)-Mn-DP-diGly});

(169) 2-(1-octafluoropentyloxyethyl)-4-ethenyl-Mn-deuteroporphynyl diglycine (hereinafter referred to as C_{5(F₈)}-Mn-DP-diGly);
 (170) 2,4-bis(1-octafluoropentyloxyethyl)-Mn-deuteroporphynyl diaspatic acid (hereinafter referred to as C_{5(F₈)}-Mn-DP-diAsp);
 5 (171) 2-(1-octafluoropentyloxyethyl)-4-ethenyl-Mn-deuteroporphynyl diaspatic acid (hereinafter referred to as C_{5(F₈)}-Mn-DP-diAsp);
 (172) 2,4-bis(1-geranyloxyethyl)-Mn-deuteroporphynyl di(p-trifluoromethyl)phenylalanylglutamic acid (hereinafter referred to as C_{10(Ger)}-Mn-DP-diPhe_(F₈)-diGlu);
 10 (173) 2,4-bis(1-dodecyloxyethyl)-Mn-deuteroporphynyl di(p-trifluoromethyl)phenylalanine (hereinafter referred to as C₁₂-Mn-DP-diPhe_(F₈));
 (174) 2,4-bis(1-dodecyloxyethyl)-Mn-deuteroporphynyl di(p-trifluoromethyl)phenylalanylglutamic acid (hereinafter referred to as C₁₂-Mn-DP-diPhe_(F₈)-diGlu);
 15 (175) 2-(1-dodecyloxyethyl)-4-ethenyl-Mn-deuteroporphynyl di(p-trifluoromethyl)phenylalanine (hereinafter referred to as C_{12(mono)}-Mn-DP-diPhe_(F₈));
 (176) Fe-protoporphynyl diglycine (hereinafter referred to as Fe-PP-diGly);
 (177) 2-[1-(2-hydroxyethoxyethyl]-4-ethenyl-Fe-deuteroporphyrin (hereinafter referred to as monoEG-Fe-DP);
 20 (178) 2-[1-(2-hydroxyethoxyethyl]-4-ethenyl-Fe-deuteroporphynyl diglycine (hereinafter referred to as monoEG-Fe-DP-diGly);
 (179) 2,4-bis[1-(2-hydroxyethoxyethyl]-Fe-deuteroporphynyl monoaspartic acid (hereinafter referred to as EG-Fe-DP-monoAsp);
 (180) 2,4-bis[1-(2-hydroxyethoxyethyl]-Fe-deuteroporphynyl diaspatic acid (hereinafter referred to as EG-Fe-DP-diAsp);
 25 (181) 2,4-bis(1-octyloxyethyl)-Fe-deuteroporphynyl diaspatic acid (hereinafter referred to as C₈-Fe-DP-diAsp);
 (182) 2,4-bis(1-decyloxyethyl)-Fe-deuteroporphynyl diaspatic acid (hereinafter referred to as C₁₀-Fe-DP-diAsp);
 (183) 2,4-bis(1-dodecyloxyethyl)-Fe-deuteroporphynyl diaspatic acid (hereinafter referred to as C₁₂-Fe-DP-diAsp);
 30 (184) 2-(1-dodecyloxyethyl)-4-ethenyl-Fe-deuteroporphynyl diaspatic acid (hereinafter referred to as C_{12(mono)}-Fe-DP-diAsp);
 (185) 2,4-bis(1-decyloxyethyl)-Co-deuteroporphynyl diaspatic acid (hereinafter referred to as C₁₀-Co-DP-diAsp);
 (186) 2,4-bis(1-dodecyloxyethyl)-Co-deuteroporphynyl diaspatic acid (hereinafter referred to as C₁₂-Co-DP-diAsp);
 35 (187) Cu-protoporphynyl monoserine (hereinafter referred to as Cu-PP-monoSer);
 (188) 2-[1-(2-hydroxyethoxyethyl]-4-ethenyl-Cu-deuteroporphyrin (hereinafter referred to as monoEG-Cu-DP);
 (189) 2,4-bis(1-octyloxyethyl)-Cu-deuteroporphynyl diaspatic acid (hereinafter referred to as C₈-Cu-DP-diAsp);
 40 (190) 2,4-bis(1-decyloxyethyl)-Cu-deuteroporphynyl diaspatic acid (hereinafter referred to as C₁₀-Cu-DP-diAsp);
 (191) 2,4-bis(1-dodecyloxyethyl)-Cu-deuteroporphynyl diaspatic acid (hereinafter referred to as C₁₂-Cu-DP-diAsp);
 45 (192) Zn-protoporphynyl monophenylalanine (hereinafter referred to as Zn-PP-monoPhe);
 (193) 2,4-bis[1-(2-hydroxyethoxyethyl]-Zn-deuteroporphyrin (hereinafter referred to as EG-Zn-DP);
 (194) 2,4-bis[1-(2-hydroxyethoxyethyl]-Zn-deuteroporphynyl dityrosine (hereinafter referred to as EG-Zn-DP-diTyr);
 (195) 2,4-bis(1-octyloxyethyl)-Zn-deuteroporphynyl diaspatic acid (hereinafter referred to as C₈-Zn-DP-diAsp);
 50 (196) 2,4-bis(1-decyloxyethyl)-Zn-deuteroporphynyl diaspatic acid (hereinafter referred to as C₁₀-Zn-DP-diAsp);
 (197) 2,4-bis(1-dodecyloxyethyl)-Zn-deuteroporphynyl diaspatic acid (hereinafter referred to as C₁₂-Zn-DP-diAsp);
 55 (198) In-protoporphynyl monotyrosine (hereinafter referred to as In-PP-monoTyr);
 (199) 2,4-bis[1-(2-hydroxyethoxyethyl]-In-deuteroporphyrin (hereinafter referred to as EG-In-DP);
 (200) 2,4-bis[1-(2-hydroxyethoxyethyl]-In-deuteroporphynyl dityrosine (hereinafter referred to as EG-In-DP-diTyr);

(201) 2,4-bis(1-octyloxyethyl)-In-deuteroporphynyl diaspatic acid (hereinafter referred to as C₈-In-DP-diAsp);

(202) 2,4-bis(1-decyloxyethyl)-In-deuteroporphynyl diaspatic acid (hereinafter referred to as C₁₀-In-DP-diAsp);

5 (203) 2,4-bis(1-dodecyloxyethyl)-In-deuteroporphynyl diaspatic acid (hereinafter referred to as C₁₂-In-DP-diAsp);

The metalloporphyrin compounds(I) of the present invention are particularly characterized in that they have at least one polyfunctional compound residue at the side chain of the porphyrin skeleton, and as a result they exert various physiological and pharmacological properties. An object of the present invention is 10 to provide metalloporphyrin derivatives for diversified uses such as treatment and diagnoses of diseases, particularly cancer, by varying the metal within the porphyrin skeleton. For instance, a metalloporphyrin derivative with a long phosphorescence life time is used as a chemical which reacts intensely to an external energy (such as laser, microwave, electromagnetic wave, supersonic wave, and medium heat), while that with short phosphorescence life time is used singly as a diagnostic agent or an anti-tumor agent. These 15 porphyrin derivatives accumulate selectively in tumor cells and are excreted therefrom very gradually. On the other hand, they are excreted from the normal organs and cells quickly and do not damage such organs and cells. Most porphyrin derivatives react intensely to light. Introduction of a polyfunctional compound residue to the side chain of a metalloporphyrin derivative according to the present invention promotes 20 excretion from the normal tissues, and offers a derivative designed to maximally utilize the manifestation of phototoxicity while leaving intact selective accumulation property in tumor cells, and a derivative designed to maximally control manifestation of phototoxicity. Based on these properties (cancer affinity, non-phototoxicity, tumor cell necrosis effect of phototoxicity combined with an external energy, tumor cell necrosis effect by single use, etc), the present invention porphyrin derivatives are most useful as 25 therapeutic and diagnostic agents for malignant tumors, as a tumor marker and as an agent for use in the missile therapy of cancers.

The compounds of the present invention are now explained in respect of their pharmacological effects and method of preparation by referring to the following examples.

30 Example 1

Laser Irradiation to the extirpated organ (excited fluorescent spectrum)

35 Golden hamsters (males, 5 per group, bodyweight approximately 150 g) were implanted subcutaneously tumor cells of the nitrosoamine-induced pancreatic cancer. After 14 to 21 days following implantation, animals were intravenously (i.v.) administered the test substance EG-Ga-DP-diGly (14) (10 mg/ml) which had been diluted with phosphate buffer at 25 mg/kg bodyweight. At 24 hours after administration, the organs including the tumor were extirpated, irradiated with N₂-pulsed laser (N₂, 337 nm, 2 ns, 400 - 1000 40 nm), and measured of excited fluorescent spectrum. The wavelengths of 600 - 900 nm were studied using the peak wavelength of NADH at 470 nm as a reference. (N₂-PLS measurement). Table 2 shows the results obtained.

45 (Tumor to tissue ratio).

Excited fluorescent spectra of the organs extirpated at 24 hours after administration were measured, and the peak wavelength at 600 - 900 nm was calculated by setting the peak wavelength at 470 nm as the reference 1. The results are shown in Table 2. As fluorescence in Mn, Fe and Cu complexes is not 50 sufficiently intense as to enable N₂-PLS measurement, the extraction method was applied to these compounds. At 24 hours following administration, the organs were extracted with an organic solvent (such as chloroform-methanol) via acetone powder, and the obtained extract was measured of UV or HPLC to calculate the tumor to tissue ratio.

As is clear from Table 2, these porphyrin related compounds were found to have a remarkable selective 55 affinity to tumor cells.

Table 2

	tumor/tissue compound	cancer/ liver	cancer/ lung	cancer/ kidney	cancer/ serum
5	(4) monoEG-Ga-DP-monoGly	1.75	2.00	3.50	2.30
10	(5) monoEG-Ga-DP-diGly	1.64	1.35	1.94	-
15	(7) monoEG-Ga-DP-monoAsp	1.39	2.10	3.58	-
20	(8) monoEG-Ga-DP-diAsp	2.30	1.50	1.32	-
25	(10) monoEG-Ga-DP-diPhe	3.39	3.98	4.13	1.60
30	(12) monoEG-Ga-DP-diTyr	2.05	2.78	3.45	1.73
35	(13) EG-Ga-DP-monoGly	2.24	1.56	2.40	1.53
40	(14) EG-Ga-DP-diGly	1.38	1.42	2.44	-
45	(15) EG-Ga-DP-monoLeu	1.00	0.81	0.90	-
50	(19) EG-Ga-DP-monoSer	2.18	0.40	3.25	0.26
55	(22) EG-Ga-DP-monoAsp	1.59	1.25	1.71	-
60	(23) EG-Ga-DP-mono[D]Asp	1.70	1.34	1.92	-
65	(24) EG-Ga-DP-diAsp	3.00	2.87	3.45	-
70	(26) EG-Ga-DP-monoGlu	2.27	3.47	5.13	-
75	(29) EG-Ga-DP-monoPhe	2.80	3.45	3.66	1.05
80	(30) EG-Ga-DP-diPhe	3.48	3.26	4.18	-
85	(31) EG-Ga-DP-monoTyr	2.94	2.60	1.19	1.42
90	(32) EG-Ga-DP-diTyr	1.93	2.13	2.31	2.10
95	(33) EG-Ga-DP-Gly·Asp	1.30	1.04	3.30	-
100	(34) EG-Ga-DP-Ser·Asp	2.50	0.93	5.05	-
105	(35) EG-Ga-DP-Asp·Phe	1.00	3.83	-	-
110	(36) EG-Ga-DP-Asp·Tyr	1.50	0.20	0.80	-
115	(44) C ₁ -Ga-DP-diAsp	1.19	0.78	2.27	2.50

50

55

	<u>compound</u>	<u>tumor/tissue</u>	cancer/ liver	cancer/ lung	cancer/ kidney	cancer/ serum
5	(45) C ₁ -Ga-DP-monoTyr		1.26	1.19	2.54	-
	(48) C ₂ -Ga-DP-diAsp		0.71	1.25	1.25	1.16
	(49) C ₃ -Ga-DP-diAsp		2.95	3.42	14.44	5.91
10	(50) C _{3(iso)} -Ga-DP-diAsp		2.63	2.33	3.03	1.54
	(51) C ₄ -Ga-DP-diAsp		3.54	4.47	7.72	2.00
	(52) C ₅ -Ga-DP-diSer		2.70	1.82	3.23	1.47
15	(53) C ₅ -Ga-DP-diAsp		4.07	3.89	6.58	0.89
	(54) C ₆ -Ga-DP-diAsp		5.33	5.33	6.86	0.98
	(55) C ₇ -Ga-DP-diAsp		2.96	2.92	4.88	0.89
20	(56) C ₈ -Ga-DP-diGly		1.69	2.44	3.03	1.92
	(57) C ₈ -Ga-DP-diSer		1.64	1.59	3.85	1.30
	(58) C ₈ -Ga-DP-diAsp		1.47	2.20	2.12	0.29
25	(59) C ₈ -Ga-DP-diTyr		1.82	2.63	3.23	0.76
	(65) C ₈ (Phenethyl)-Ga-DP-diAsp		3.79	2.89	3.79	0.72
	(66) C ₉ -Ga-DP-diAsp		2.07	3.40	3.54	1.12
30	(68) C ₁₀ -Ga-DP-diAsp		11.54	23.08	16.44	2.78
	(70) C ₁₀ (Gera)-Ga-DP-diAsp		3.33	4.88	3.82	2.19
	(72) C ₁₀ (Citro)-Ga-DP-diAsp		11.37	12.39	15.66	2.82
35	(74) C _{10(H2Citro)} -Ga-DP-diAsp		9.09	11.11	11.49	3.50
	(77) C ₁₂ -Ga-DP-diAsp		4.38	7.00	8.54	1.35
	(78) C ₁₂ -Ga-DP-diGlu		2.00	4.00	4.00	-
40	(99) monoEG-Mn-DP-diGly		1.03	2.35	2.43	1.50

45 Example 2

In vivo hemorrhagic necrosis effect on the nitrosoamine-induced pancreatic cancer

50 Cancer bearing hamsters of Example 1 were i.v. administered the test substance C₆-Ga-DP-diAsp (54) (10 mg/ml) which had been diluted with phosphate buffer at 25 mg/kg bodyweight and 12.5 mg/kg bodyweight respectively. The animals were exsanguinated and autopsied at 24 hours after administration, and observed. The cancer mass of the treatment group developed hemorrhagic necrosis as shown in Figs. 1, 2 and 3. The organs such as the liver, lungs, kidneys of the treated group excluding the tumor and those of the control group (the group which was not administered the test substance) showed no changes.

55 Anti-tumor effect of the test material was evaluated by the intensity of hemorrhagic necrosis at 24 hours following administration of the test substance in the manner mentioned above and by the pathological study discussed in Example 3. The evaluation was based on the four scales of G₄, G₃, G₂ and G₁. The result is

shown in Table 3.

5

10

15

20

25

30

35

40

45

50

55

Table 3

	Compound	Hemorrhagic necrosis effect
5	(7) monoEG-Ga-DP-monoAsp	G ₁
10	(8) monoEG-Ga-DP-diAsp	G ₁
15	(15) EG-Ga-DP-monoLeu	G ₁
20	(22) EG-Ga-DP-monoAsp	G ₂
25	(23) EG-Ga-DP-mono[D]Asp	G ₂
30	(26) EG-Ga-DP-monoGlu	G ₁
35	(33) EG-Ga-DP-Gly·Asp.	G ₂
40	(34) EG-Ga-DP-Ser·Asp	G ₁
45	(35) EG-Ga-DP-Asp·Phe	G ₁
50	(36) EG-Ga-DP-Asp·Tyr	G ₁
55	(37) MC-Ga-DP-monoSer	G ₂
60	(38) MC-Ga-DP-monoAsp	G ₁
65	(40) EC-Ga-DP-monoAsp	G ₁
70	(43) C ₁ -Ga-DP-monoAsp	G ₁
75	(44) C ₁ -Ga-DP-diAsp	G ₁
80	(47) C ₂ -Ga-DP-monoAsp	G ₁
85	(48) C ₂ -Ga-DP-diAsp	G ₁
90	(49) C ₃ -Ga-DP-diAsp	G ₂
95	(50) C _{3(iso)} -Ga-DP-diAsp	G ₂
100	(51) C ₄ -Ga-DP-diAsp	G ₄
105	(52) C ₅ -Ga-DP-diSer	G ₁
110	(53) C ₅ -Ga-DP-diAsp	G ₄
115	(54) C ₆ -Ga-DP-diAsp	G ₄
120	(55) C ₇ -Ga-DP-diAsp	G ₄
125	(56) C ₈ -Ga-DP-diGly	G ₁
130	(57) C ₈ -Ga-DP-diSer	G ₁
135	(58) C ₈ -Ga-DP-diAsp	G ₃
140	(59) C ₈ -Ga-DP-diTyr	G ₁
145	(65) C _{8(phenethyl)} -Ga-DP-diAsp	G ₁
150	(66) C ₉ -Ga-DP-diAsp	G ₂
155	(68) C ₁₀ -Ga-DP-diAsp	G ₂
160	(70) C _{10(Gera)} -Ga-DP-diAsp	G ₂
165	(72) C _{10(Citro)} -Ga-DP-diAsp	G ₂

	Compound	Hemorrhagic necrosis effect
5	(74) C ₁₀ (H ₂ Citro)-Ga-DP-diAsp	G ₂
10	(76) C ₁₂ -Ga-DP-diGly	G ₁
15	(77) C ₁₂ -Ga-DP-diAsp	G ₂
20	(78) C ₁₂ -Ga-DP-diGlu	G ₁
25	(108) EG-Mn-DP-monoAsp	G ₁
30	(115) C ₈ -Mn-DP-diGly	G ₁
35	(116) C ₈ -Mn-DP-diAsp	G ₃
40	(117) C ₁₀ -Mn-DP-diGly	G ₁
45	(122) C ₁₀ -Mn-DP-diAsp	G ₃
50	(123) C ₁₀ -Mn-DP-d[D]Asp	G ₃
55	(124) C ₁₀ -Mn-DP-diGlu	G ₁
60	(126) C ₁₀ -Mn-DP-diGly-diAsp	G ₂
65	(127) C ₁₀ -Mn-DP-diLeu-diAsp	G ₂
70	(128) C ₁₀ -Mn-DP-diPhe-diAsp	G ₂
75	(132) C ₁₀ (Gera)-Mn-DP-diAsp	G ₃
80	(134) C ₁₀ (Citro)-Mn-DP-monoAsp	G ₂
85	(135) C ₁₀ (Citro)-Mn-DP-diAsp	G ₃
90	(137) C ₁₀ (H ₂ Citro)-Mn-DP-diAsp	G ₄
95	(138) C ₁₀ (H ₂ Citro,mono)-Mn-DP-diAsp	G ₂
100	(143) C ₁₂ -Mn-DP-diAsp	G ₄
105	(145) C ₁₂ -Mn-DP-diAsp-tetraGly	G ₂
110	(147) C ₁₂ (mono)-Mn-DP-diAsp	G ₂
115	(149) C ₁₄ -Mn-DP-diAsp	G ₃
120	(154) C ₁₈ -Mn-DP-diAsp-tetraAsp	G ₂
125	(160) H ₄ Fran-Mn-DP-diAsp	G ₂
130	(164) Nct-Mn-DP-diAsp	G ₂
135	(181) C ₈ -Fe-DP-diAsp	G ₃
140	(183) C ₁₂ -Fe-DP-diAsp	G ₃
145	(185) C ₁₀ -Co-DP-diAsp	G ₁
150	(186) C ₁₂ -Co-DP-diAsp	G ₁
155	(191) C ₁₂ -Cu-DP-diAsp	G ₁
160	(197) C ₁₂ -Zn-DP-diAsp	G ₂

Pathology

Tumor bearing hamsters of Example 1 were treated similarly as in Example 2 except that they were administered C₁₂-Mn-DP-diAsp (143) instead of C₆-Ga-DP-diAsp (54). Organs including the tumor (the 5 treated group and the control group) were fixed with formalin, embedded in paraffin, cut into sections, double stained with hematoxylin-eosin, and observed pathologically.

Figs. 4 and 5 show photographs of the tumor cell necrosis of the treated group. There were many cell necrosis images and necrotic layers which were not present in the non-cancerous organs and the control group.

10

Example 4

15 In vivo cell growth inhibition effect

Tumor bearing hamsters of Example 1 were i.v. administered the test substance C₁₀-Mn-DP-diAsp (122) (10 mg/ml) diluted by phosphate buffer at 25 mg/kg bodyweight. The tumor size was measured supracutaneously using slide calipers on an appropriate day following administration.

20

Method of calculation

$$\text{Volume} = \frac{1}{2} \times (\text{long diameter}) \times (\text{short diameter})^2$$

25 Fig. 6 shows tumor cell growth curves of the groups administered C₁₀-Mn-DP-diAsp (122) and C₁₂-Mn-DP-diAsp (143), and the control group. As is clear from these curves, both treated groups manifested notable tumor growth inhibitory effect compared to the control group, indicating the test substances had carcinostatic activities.

30

Example 5

In vitro photosensitivity test

35

Leukemia cells of a mouse (P388) were placed in wells (a plate with 24 wells) at 5×10^4 /well, and incubated for 2 hours. The test materials C₆-Ga-DP-diAsp (58), C₁₀-Mn-DP-diAsp (122) and photofrin II each at concentrations of 1.56, 3.13, 6.25, 12.5, 25, and 50 ng/ml (common ratio : 2) were prepared. The specified amounts of these test solutions were added to the above culture, irradiated at 10,000 lux for 1 hour, incubated for 48 hours, and the cells per one well were counted. A group shielded from light using an aluminium foil during irradiation was provided as control. The index of photosensitivity was obtained by dividing the cell counts of the respective groups with the cell count of an untreated group provided separately (cell growth inhibition ratio (%)).

40 Fig. 7 shows the cell growth inhibition ratio. As is clear from the figure, the irradiated groups treated with Ga complex showed a higher inhibition ratio compared to the control group, manifesting photosensitivity at 1.0 ng/ml or above. As for the groups treated with Mn complex, there was observed no distinct difference in inhibition ratio between the treated groups and the control group, thus indicating no photosensitivity. The inhibition ratio was observed to elevate at concentration of 12.5 ng/ml or higher for each of the test materials. However, this was attributed to the toxicity of the test material per se rather than 45 to irradiation.

Example 6

55

In vivo irradiation therapy using Yag laser

Tumor bearing hamsters of Example 1 were i.v. administered the test materials C₆-Ga-DP-diAsp (54)

and C₁₀-Ga-DP-diAsp (68) (10 mg/ml) at 12.5 mg/kg bodyweight. At 24 hours after administration, the hair above the tumor site was shaved and irradiation with Yag laser commenced (1064 nm, 5 w, 10 sec x 4). At 24 hours following irradiation, the animals were exsanguinated and autopsied for observation. As is clear from Figs. 8 and 9, the cancer mass of the groups administered the test materials was necrotic, while that of the control group (untreated group) showed no such changes.

It is therefore clear that the present invention substance is effective for a therapy using an external energy such as Yag laser.

10 Example 7

To 1 g of DCHA salt of Ga-protoporphyrin (hereinafter referred to as DCHA salt of Ga-PP) were added and dissolved 60 ml of chloroform and 10 ml of tetrahydrofuran. To the resultant solution was added 0.5 g of glycine ethyl ester hydrochloride (hereinafter referred to as Gly(OEt)[•]HCl). The obtained solution was then gradually added with 0.1 g of WSC while stirring, and reacted for 2 hours. After the reaction was completed [confirmed by TLC [chloroform : methanol (4 : 1)]], the reaction solution was washed with water to recover the unreacted substance. After separation, the chloroform layer was concentrated. The obtained concentrate was recrystallized with ethanol ethyl acetate to obtain 0.12 g of Ga-PP-monoGly(OEt) (ethyl ester of 1). The yield was 16.4%.

20

Example 8

To 0.1 g of ethyl ester of 1 was added 1/2 N KOH alcohol until the hydrolysis reaction was completed. After the reaction was completed (confirmed by TLC), 10% citric acid solution was added to adjust pH to 5.5, and the resultant solution was extracted with chloroform and concentrated. The resultant concentrate was recrystallized with methanol ethyl acetate to obtain 0.11 g of Ga-PP-monoGly (1). The yield was 98.0%.

30 Example 9

To 0.38 g of DCHA salt of Ga-PP were added and dissolved 10 ml of chloroform and 3 ml of acetonitrile. To the resultant solution were added 0.38 g of tyrosine methyl ester hydrochloride (hereinafter referred to as Tyr(OMe)[•]HCl), and then gradually 0.38 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.22 g of Ga-PP-diTyr (3). The yield was 60.0%.

Example 10

40

To 2 g of DCHA salt of 2[1-(2-hydroxyethoxy)ethyl]-4-ethenyl-deuteroporphyrin (hereinafter referred to as DCHA salt of monoEG-Ga-DP) were added and dissolved 300 ml of chloroform and 150 ml of acetonitrile. To the resultant solution were added 2 g of Gly(OEt)[•]HCl dissolved in 20 ml of water, and then gradually 14 ml of 10% WSC chloroform solution while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.11 g of monoEG-Ga-DP-monoGly (4). The yield was 7.4%.

Example 11

50

To 1.6 g of DCHA salt of monoEG-Ga-DP were added and dissolved 60 ml of chloroform and 30 ml of acetonitrile. To the resultant solution were added 0.75 g of Gly(OEt)[•]HCl, and then gradually 1.3 g of dicyclohexylcarbodiimide (hereinafter referred to as DDC) while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 1.11 g of monoEG-Ga-DP-diGly (5). The yield was 89.8%.

55

Example 12

To 1 g of DCHA salt of monoEG-Ga-DP were added and dissolved 10 ml of chloroform and 20 ml of acetonitrile. To the resultant solution were added 2 g of aspartic acid dimethyl ester hydrochloride (hereinafter referred to as Asp(OMe)[•]HCl) dissolved in 0.5 ml of dimethylformamide (hereinafter referred to as DMF), and then gradually 2 ml of 5% WSC chloroform solution while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.25 g of monoEG-Ga-DP-monoAsp (7). The yield was 32.3%.

Example 13

To 5 g of DCHA salt of monoEG-Ga-DP were added and dissolved 50 ml of chloroform and 100 ml of acetonitrile. To the resultant solution were added 5 ml of 50% Asp(OMe)[•]HCl DMF solution, and then gradually 3.2 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 3.8 g of monoEG-Ga-DP-diAsp (8). The yield was 86.5%.

15

Example 14

To 10 g of DCHA salt of monoEG-Ga-DP were added and dissolved 280 ml of chloroform and 140 ml of acetonitrile. To the resultant solution were added 10 g of phenylalanine methyl ester hydrochloride (hereinafter referred to as Phe(OMe)[•]HCl), and then gradually 8 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 8.3 g of monoEG-Ga-DP-diPhe (10). The yield was 89.8%.

25

Example 15

To 3 g of DCHA salt of monoEG-Ga-DP were added and dissolved 150 ml of chloroform and 150 ml of acetonitrile. To the resultant solution were added 3 g of Tyr(OMe)[•]HCl dissolved in 3 ml of water, and then gradually 1 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.62 g of monoEG-Ga-DP-monoTyr (11). The yield was 24.9%.

35

Example 16

To 1.07 g of DCHA salt of monoEG-Ga-DP were added and dissolved 45 ml of chloroform and 15 ml of acetonitrile. To the resultant solution were added 1 g of Tyr(OMe)[•]HCl, and then gradually 1 of DCC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 1.01 g of monoEG-Ga-DP-diTyr (12). The yield was 97.6%.

40

Example 17

To 150 g of Ga-protoporphyrin dimethyl ester (hereinafter referred to as Ga-PP-Me) was added 1.5 liter of 6% hydrobromic acid/acetic acid (hereinafter referred to as HBr/HOAc). The resultant solution was left standing for 24 hours, concentrated under reduced pressure at below 50 °C, and the Br derivatives obtained as a result of concentration was added with ethyleneglycol and left standing for 24 hours. After reaction was completed (confirmed by TLC), the product was washed with water, hydrolyzed and recrystallized (acetone-ethyl acetate) to obtain 90 g of 2,4-bis[1-(2-hydroxyethoxy)ethyl]-Ga-deutroporphyrin (hereinafter referred to as EG-Ga-DP). The yield was 50.6%.

50

Example 18

To 1 g of DCHA salt of EG-Ga-DP obtained in Example 17 were added and dissolved 100 ml of chloroform and 100 ml of acetonitrile. To the resultant solution were added 1 g of Gly(OEt)[•]HCl dissolved in 10 ml of water, and then gradually 10 ml of 10% WSC chloroform solution while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.2 g of EG-Ga-DP-monoGly (13).

The yield was 27.2%.

Example 19

To 0.5 g of DCHA salt of EG-Ga-DP were added and dissolved 20 ml of chloroform and 10 ml of acetonitrile. To the resultant solution were added 0.25 g of Gly(OEt)^{*}HCl, and then gradually 0.4 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.28 g of EG-Ga-DP-diGly (14). The yield was 71.4%.

10

Example 20

To 2 g of DCHA salt of EG-Ga-DP were added and dissolved 20 ml of chloroform and 60 ml of acetonitrile. To the resultant solution were added 1 g of leucine methyl ester hydrochloride (hereinafter referred to as Leu(OMe)^{*}HCl) dissolved in 5 ml of DMF, and then gradually 2 ml of 3% WSC chloroform solution while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.15 g of EG-Ga-DP-monoLeu (15). The yield was 9.6%.

20

Example 21

To 2 g of DCHA salt of EG-Ga-DP were added and dissolved 20 ml of chloroform and 60 ml of acetonitrile. To the resultant solution were added 1 g of Leu(OMe)^{*}HCl dissolved in 5 ml of DMF, and then gradually 2 ml of 3% WSC chloroform solution while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.21 g of EG-Ga-DP-diLeu (16). The yield was 11.9%.

Example 22

30

To 2 g of DCHA salt of EG-Ga-DP were added and dissolved 30 ml of chloroform and 30 ml of acetonitrile. To the resultant solution were added 1 g of serine methyl ester hydrochloride (hereinafter referred to as Ser(OMe)^{*}HCl) dissolved in 4 ml of DMF, and then gradually 6 ml of 6% WSC chloroform solution while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.49 g of EG-Ga-DP-monoSer (19). The yield was 11.8%.

Example 23

40

To 25 g of DCHA salt of EG-Ga-DP were added and dissolved 250 ml of chloroform and 500 ml of acetonitrile. To the resultant solution were added 12 g of Asp(OMe)^{*}HCl dissolved in 13 ml of DMF, and then gradually 32.5 ml of 10% WSC chloroform solution while stirring. When the reaction was completed after 70 minutes (confirmed with TLC), the reaction liquid was washed with water, extracted and divided with 4% NaHCO₃ solution, and added with 10% citric acid solution to the water layer to adjust pH to 5.5. The pH-adjusted water layer was extracted with chloroform and concentrated under reduced pressure to obtain 6.63 g of methyl ester of EG-Ga-DP-monoAsp (22). By concentrating the chloroform layer under reduced pressure, 2.3 g of methyl ester of EG-Ga-DP-diAsp (24) was also obtained. Hydrolysis was performed similarly as in Example 8 on 0.1 g each of esters to obtain 70 mg of EG-Ga-DP-monoAsp (22) and 50 mg of EG-Ga-DP-diAsp (24). The yields were 23.6% and 5.2% respectively.

50

Example 24

55

To 5 g of DCHA salt of EG-Ga-DP were added and dissolved 50 ml of chloroform and 100 ml of acetonitrile. To the resultant solution were added 2.5 g of [D]Asp(OMe)^{*}HCl dissolved in 2.5 ml of DMF, and then gradually 18 ml of 5% WSC chloroform solution while cooling and stirring. The procedure similar to that of Example 23 was thereafter followed to obtain 0.75 g of EG-Ga-DP-mono[D]Asp (23). The yield was 20.1%.

Example 25

To 1 g of DCHA salt of EG-Ga-DP were added and dissolved 10 ml of chloroform and 20 ml of acetonitrile. To the resultant solution were added 0.5 g of glycamic acid diethyl ester hydrochloride (hereinafter referred to as Glu(OEt)[•]HCl) dissolved in 0.5 ml of DMF, and then gradually 4 ml of 5% WSC chloroform solution while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 42 mg of EG-Ga-DP-monoGlu (26). The yield was 5.27%.

10 Example 26

To 0.5 g of DCHA salt of EG-Ga-DP were added and dissolved 12 ml of chloroform and 20 ml of acetonitrile. To the resultant solution were added 0.5 g of lysine methyl ester hydrochloride (hereinafter referred to as Lys(OMe)[•]HCl) dissolved in 10 ml of DMF, and then gradually 5 ml of 10% WSC chloroform solution while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 80 mg of EG-Ga-DP-monoLys (28). The yield was 20.1%.

Example 27

20 To 0.5 g of DCHA salt of EG-Ga-DP were added and dissolved 30 ml of chloroform and 30 ml of acetonitrile. To the resultant solution were added 0.5 g of Phe(OMe)[•]HCl dissolved in 30 ml of water, and then gradually 5 ml of 10% WSC chloroform solution while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.24 g of EG-Ga-DP-monoPhe (29). The yield was 59.0%.

Example 28

30 To 0.5 g of DCHA salt of EG-Ga-DP were added and dissolved 40 ml of chloroform and 13 ml of acetonitrile. To the resultant solution were added 0.5 g of Phe(OMe)[•]HCl, and then gradually 5 ml of 10% WSC chloroform solution while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.38 g of EG-Ga-DP-diPhe (30). The yield was 80.8%.

35 Example 29

To 5 g of EG-Ga-DP were added and dissolved 150 ml of chloroform, 25 ml of acetonitrile, and 15 ml of DMF. To the resultant solution were added 5 g of Tyr(OMe)[•]HCl dissolved in 15 ml of DMF, and then gradually 15 ml of 5% DCC chloroform solution while stirring. The procedure similar to that of Example 8 was thereafter followed to obtain 1.4 g of EG-Ga-DP-monoTyr (31). The yield was 23.2%.

Example 30

45 To 1 g of DCHA salt of EG-Ga-DP were added and dissolved 40 ml of chloroform and 20 ml of acetonitrile. To the resultant solution were added 1 g of Tyr(OMe)[•]HCl, and then gradually 1 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.78 g of EG-Ga-DP-diTyr (32). The yield was 80.5%.

50

Example 31

To 0.2 g of DCHA salt of EG-Ga-DP-monoGly (13) ethyl ester obtained in Example 18 were added and dissolved 8 ml of chloroform and 4 ml of acetonitrile. To the resultant solution were added 0.2 g of Asp(OMe)[•]HCl, and then gradually 0.2 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.11 g of EG-Ga-DP-Gly[•]Asp (33). The yield was 62.8%.

Example 32

To 0.2 g of DCHA salt of EG-Ga-DP-monoAsp (22) methyl ester obtained in Example 23 were added and dissolved 8 ml of chloroform and 4 ml of acetonitrile. To the resultant solution were added 0.2 g of Ser-(OMe)*HCl, and then gradually 0.3 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 70 mg of EG-Ga-DP-Ser*Asp (34). The yield was 39.3%.

Example 33

To 0.2 g of DCHA salt of EG-Ga-DP-monoAsp (22) methyl ester obtained in Example 23 were added and dissolved 8 ml of chloroform and 4 ml of acetonitrile. To the resultant solution were added 0.2 g of Phe-(OMe)*HCl, and then gradually 0.2 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.17 g of EG-Ga-DP-Asp*Phe (35). The yield was 61.8%.

15

Example 34

To 0.2 g of DCHA salt of EG-Ga-DP-monoTyr (31) methyl ester obtained in Example 29 were added and dissolved 8 ml of chloroform and 4 ml of acetonitrile. To the resultant solution were added 0.2 g of Asp-(OMe)*HCl, and then gradually 0.2 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.1 g of EG-Ga-DP-Asp*Tyr (36). The yield was 52.9%.

25 Example 35

The procedure similar to Example 17 was followed using 10 g of Ga-PP-Me and 100 ml of 6% HBr/HOAc, and 50 ml each of methyl cellosolve and ethyl cellosolve (hereinafter respectively referred to as MC and EC) instead of ethylene glycol. There were obtained 2.3 g and 1.63 g of 2,4-bis[1-(2-methoxyethoxyethyl]-Ga-deuteroporphyrin and 2,4-bis[1-(2-ethoxyethoxyethyl]-Ga-deuteroporphyrin (hereinafter respectively referred to as MC-Ga-DP and EC-Ga-DP). The yields were 28.1% and 12.8% respectively.

35 Example 36

To 0.8 g of DCHA salt of MC-Ga-DP obtained in Example 35 were added and dissolved 8 ml of chloroform and 16 ml of acetonitrile. To the resultant solution were added 0.4 g of Asp(OMe)*HCl dissolved in 0.4 ml of DMF, and then gradually 3 ml of 5% WSC chloroform solution while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.13 g of MC-Ga-DP-monoAsp (38). The yield was 20.5%.

Example 37

45

To 0.8 g of DCHA salt of EC-Ga-DP obtained in Example 35 were added and dissolved 8 ml of chloroform and 16 ml of acetonitrile. To the resultant solution were added 0.4 g of Asp(OMe)*HCl dissolved in 0.4 ml of DMF, and then gradually 1 ml of 5% WSC chloroform solution while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.21 g of EC-Ga-DP-monoAsp (40). The yield was 33.0%.

Example 38

55 The procedure similar to Example 17 was followed using 6 g of Ga-PP-Me and 60 ml of 10% HBr/HOAc, and 30 ml each of methyl alcohol, ethyl alcohol, propyl alcohol, isopropyl alcohol, butyl alcohol, pentyl alcohol, hexyl alcohol, heptyl alcohol, octyl alcohol, nonyl alcohol, decyl alcohol and dodecyl alcohol separately instead of ethylene glycol. After hydrolysis, the first two were recrystallized (methanol - ethyl

acetate) and the remaining ten were passed through silica gel column chromatography (ethyl acetate - hexane) and recrystallized to obtain respectively 1.0 g, 0.45 g, 2.7 g, 1.3 g, 2.8 g, 2.0 g, 1.6 g, 4.0 g, 1.4 g, 0.84 g, 0.68 g and 2.0 g of 2,4-bis(1-methoxyethyl)-Ga-deuteroporphyrin, 2,4-bis(1-ethoxyethyl)-Ga-deuteroporphyrin, 2,4-bis(1-propoxyethyl)-Ga-deuteroporphyrin, 2,4-bis(1-isopropoxyethyl)-Ga-deuteroporphyrin, 2,4-bis(1-butoxyethyl)-Ga-deuteroporphyrin, 2,4-bis(1-pentyloxyethyl)-Ga-deuteroporphyrin, 2,4-bis(1-hexyloxyethyl)-Ga-deuteroporphyrin, 2,4-bis(1-heptyloxyethyl)-Ga-deuteroporphyrin, 2,4-bis(1-octyloxyethyl)-Ga-deuteroporphyrin, and 2,4-bis(1-nonyloxyethyl)-Ga-deuteroporphyrin, 2,4-bis(1-decyloxyethyl)-Ga-deuteroporphyrin (hereinafter respectively referred to as C₁-Ga-DP, C₂-Ga-DP, C₃-Ga-DP, C_{3(iso)}-Ga-DP, C₄-Ga-DP, C₅-Ga-DP, C₆-Ga-DP, C₇-Ga-DP, C₈-Ga-DP, C₉-Ga-DP, C₁₀-Ga-DP and C₁₂-GA-DP). The yields were respectively 15.2%, 6.6%, 38.0%, 18.4%, 38.1%, 26.4%, 20.4%, 49.9%, 16.4%, 9.8%, 7.5% and 21.3%.

Example 39

To 0.5 g of DCHA salt of C₁-Ga-DP obtained in Example 38 were added and dissolved 5 ml of chloroform and 2 ml of acetonitrile. To the resultant solution were added 0.5 g of Asp(OMe)^{*}HCl and then gradually 0.51 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.44 g of C₁-Ga-DP-diAsp (44). The yield was 100%.

To 0.5 g of DCHA salt of C₁-Ga-DP were added and dissolved 30 ml of chloroform and 30 ml of acetonitrile. To the resultant solution were added 0.5 g of Tyr(OMe)^{*}HCl dissolved in 3.5 ml of water, and then gradually 3 ml of 10% WSC chloroform solution while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.14 g of C₁-Ga-DP-monoTyr (45). The yield was 34.3%.

Example 41

To 0.5 g of DCHA salt of C₂-Ga-DP obtained in Example 38 were added and dissolved 5 ml of chloroform and 2 ml of acetonitrile. To the resultant solution were added 0.5 g of Asp(OMe)^{*}HCl, and then gradually 0.47 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.42 g of C₂-Ga-DP-diAsp (48). The yield was 95.2%.

Example 42

To 0.5 g of DCHA salt of C₃-Ga-DP obtained in Example 38 were added and dissolved 5 ml of chloroform and 2.5 ml of acetonitrile. To the resultant solution were added 0.75 g of Asp(OMe)^{*}HCl, and then gradually 0.52 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.32 g of C₃-Ga-DP-diAsp (49). The yield was 72.2%.

To 0.2 g of DCHA salt of C_{3(iso)}-Ga-DP obtained in Example 38 were added and dissolved 4.5 ml of chloroform and 1.5 ml of acetonitrile. To the resultant solution were added 0.2 g of Asp(OMe)^{*}HCl, and then gradually 0.31 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.11 g of C_{3(iso)}-GA-DP-diAsp (50). The yield was 62.2%.

Example 44

To 0.5 g of DCHA salt of C₄-Ga-DP obtained in Example 38 were added and dissolved 5 ml of chloroform and 2.5 ml of acetonitrile. To the resultant solution were added 0.75 g of Asp(OMe)^{*}HCl, and

then gradually 0.59 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.44 g of C₄-Ga-DP-diAsp (51). The yield was 100%.

5 Example 45

To 0.3 g of DCHA salt of C₅-Ga-DP obtained in Example 38 were added and dissolved 6 ml of chloroform and 3 ml of acetonitrile. To the resultant solution were added 0.2 g of Ser(OMe)[•]HCl, and then gradually 4 ml of 5% WSC chloroform solution while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.22 g of C₅-Ga-DP-diSer (52). The yield was 86.8%.

Example 46

15 To 0.2 g of DCHA salt of C₅-Ga-DP were added and dissolved 4.5 ml of chloroform and 1.5 ml of acetonitrile. To the resultant solution were added 0.2 g of Asp(OMe)[•]HCl, and then gradually 0.25 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.17 g of C₅-Ga-DP-diAsp (53). The yield was 95.5%.

20 Example 47

To 0.75 g of DCHA salt of C₆-Ga-DP obtained in Example 38 were added and dissolved 14 ml of chloroform and 7 ml of acetonitrile. To the resultant solution were added 1 g of Asp(OMe)[•]HCl, and then gradually 0.68 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.5 g of C₆-Ga-DP-diAsp (54). The yield was 74.6%.

Example 48

30 To 0.43 g of DCHA salt of C₇-Ga-DP obtained in Example 38 were added and dissolved 4 ml of chloroform and 2 ml of acetonitrile. To the resultant solution were added 0.44 g of Asp(OMe)[•]HCl, and then gradually 0.59 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.34 g of C₇-Ga-DP-diAsp (55). The yield was 88.3%.

35 Example 49

40 To 2 g of DCHA salt of C₈-Ga-DP obtained in Example 38 were added and dissolved 45 ml of chloroform and 15 ml of acetonitrile. To the resultant solution were added 2 g of Gly(OEt)[•]HCl, and then gradually 1 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.4 g of C₈-Ga-DP-diGly (56). The yield was 26.8%.

45 Example 50

To 1 g of DCHA salt of C₈-Ga-DP were added and dissolved 15 ml of chloroform and 15 ml of acetonitrile. To the resultant solution were added 0.5 g of Ser(OMe)[•]HCl, and then gradually 10 ml of 5% WSC chloroform solution while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.74 g of C₈-Ga-DP-diSer (57). The yield was 86.5%.

Example 51

55 To 1.5 g of DCHA salt of C₈-Ga-DP were added and dissolved 80 ml of chloroform and 30 ml of acetonitrile. To the resultant solution were added 2 g of Asp(OMe)[•]HCl, and then gradually 1 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.16 g of C₈-Ga-DP-diAsp (58). The yield was 12.7%.

Example 52

To 1.5 g of DCHA salt of C₈-Ga-DP were added and dissolved 45 ml of chloroform and 15 ml of acetonitrile. To the resultant solution were added 1.5 g of Tyr(OMe)^{*}HCl, and then gradually 1 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.28 g of C₈-Ga-DP-diTyr (59). The yield was 20.3%.

Example 53

The procedure similar to that of Example 17 was followed using 6 g of Ga-PP-Me and 60 ml of 3% HBr/HOAc, and 30 ml of octyl alcohol instead of ethylene glycol. After hydrolysis, the resultant substance was passed through silica gel column chromatography (ethyl acetate -hexane), and recrystallized to obtain 0.98 g of the mixture of C₈-Ga-DP and 2-(1-octyloxyethyl)-4-ethenyl-Ga-deuteroporphyrin (hereinafter referred to as C₈(mono)-Ga-DP). The yield was 11.7%.

Example 54

To 2 g of DCHA salt of the C₈-Ga-DP and C₈(mono)-Ga-DP mixture obtained in Example 53 were added 45 ml of chloroform and 45 ml of acetonitrile. To the resultant solution were added 2 g of Gly(OEt)^{*}HCl, and then gradually 1 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain Gly derivative mixture. The mixture was then passed through OS (C₈) high performance liquid chromatography [eluent, MeOH-H₂O (9:1)] to obtain 0.005 g of C₈(mono)-Ga-diGly (60). The yield was 0.3%.

Example 55

To 6 g of DCHA salt of the mixture of C₈-Ga-DP and C₈(mono)-Ga-DP was added and dissolved 120 ml of chloroform. To the resultant solution were added 8 g of Asp(OMe)^{*}HCl, and then gradually 5.5 g of WSC while stirring. The procedure similar to those of Examples 7, 8 and 54 was thereafter followed to obtain 0.3 g of C₈(mono)-Ga-diAsp (62). The yield was 6.3%.

Example 56

To 1.5 g of DCHA salt of the mixture of C₈-Ga-DP and C₈(mono)-Ga-DP were added and dissolved 45 ml of chloroform and 15 ml of acetonitrile. To the resultant solution were added 1.5 g of Tyr(OMe)^{*}HCl, and then gradually 1 g of WSC while stirring. The procedure similar to those of Examples 7, 8 and 54 was thereafter followed to obtain 0.013 g of C₈(mono)-Ga-diTyr (63). The yield was 0.9%.

Example 57

The procedure similar to Example 17 was followed using 6 g of Ga-DP-Me and 60 ml of 10% HBr/HOAc, and 30 ml of phenethyl alcohol instead of ethylene glycol. After hydrolysis, the resultant substance was passed through silica gel column chromatography (ethyl acetate - hexane) and recrystallized to obtain 2.9 g of C₈(phenethyl)-Ga-DP (64). The yield was 66.1%.

50

Example 58

To 0.2 g of DCHA salt of (64) obtained in Example 57 were added and dissolved 4.5 ml of chloroform and 1.5 ml of acetonitrile. To the resultant solution were added 0.2 g of Asp(OMe)^{*}HCl, and then gradually 0.25 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.06 g of C₈(phenethyl)-Ga-DP-diAsp (65). The yield was 33.5%.

Example 59

To 0.17 g of DCHA salt of C₉-Ga-DP obtained in Example 38 were added and dissolved 10 ml of chloroform and 5 ml of acetonitrile. To the resultant solution were added 0.2 g of Asp(OMe)•HCl, and then 5 gradually 0.27 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.15 g of C₉-Ga-DP-diAsp (66). The yield was 98.0%.

Example 60

10 To 0.38 g of DCHA salt of C₁₀-Ga-DP obtained in Example 38 were added and dissolved 8 ml of chloroform and 3 ml of acetonitrile. To the resultant solution were added 0.2 g of Ser(OMe)•HCl, and then gradually 4 ml of 5% WSC chloroform solution while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.29 g of C₁₀-Ga-DP-diSer (67). The yield was 88.6%.

15

Example 61

20 To 0.54 g of DCHA salt of C₁₀-Ga-DP were added and dissolved 10 ml of chloroform and 5 ml of acetonitrile. To the resultant solution were added 0.54 g of Asp(OMe)•HCl, and then gradually 0.54 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.48 g of C₁₀-Ga-DP-diAsp (68). The yield was 98.4%.

25 Example 62

The procedure similar to Example 17 was followed using 4.5 g of Ga-PP-Me and 45 ml of 10% HBr/HOAc, and 25 ml of geraniol instead of ethylene glycol. After hydrolysis, the resultant substance was passed through silica gel column chromatography (ethyl acetate - hexane), and recrystallized to obtain 1.0 g of C_{10(Gera)}-Ga-DP (69). The yield was 15.2%.

Example 63

35 To 0.5 g of DCHA salt of (69) were added and dissolved 10 ml of chloroform and 5 ml of acetonitrile. To the resultant solution were added 0.5 g of Asp(OMe)•HCl, and then gradually 0.73 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.42 g of C_{10(Gera)}-Ga-DP-diAsp (70). The yield was 93.1%.

40

Example 64

The procedure similar to those of Examples 17 and 62 was followed using 3 g of Ga-PP-Me and 30 ml of 10% HBr/HOAc, and 18 ml of citronellol instead of ethylene glycol to obtain 1.4 g of C_{10(Citro)}-Ga-DP (71). 45 The yield was 31.8%.

Example 65

50 To 0.5 g of DCHA salt of (71) were added and dissolved 10 ml of chloroform and 5 ml of acetonitrile. To the resultant solution were added 0.5 g of Asp(OMe)•HCl, and then gradually 0.72 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.43 g of C_{10(Citro)}-Ga-DP-diAsp (72). The yield was 95.3%.

55

Example 66

The procedure similar to Examples 17 and 62 was followed using 3 g of Ga-PP-Me and 30 ml of 10%

HBr/HOAc, and 18 ml of dihydrocitronellol instead of ethylene glycol to obtain 1.1 g of $C_{10}(H_2\text{Citro})\text{-Ga-DP}$ (73). The yield was 24.8%.

5 Example 67

To 0.5 g of DCHA salt of (73) were added and dissolved 10 ml of chloroform and 5 ml of acetonitrile. To the resultant solution were added 0.5 g of Asp(OMe) \cdot HCl, and then gradually 0.72 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.42 g of $C_{10}(H_2\text{Citro})\text{-Ga-DP-diAsp}$ (74). The yield was 93.8%.

Example 68

15 To 1 g of DCHA salt of $C_{12}\text{-Ga-DP}$ obtained in Example 38 were added and dissolved 20 ml of chloroform and 10 ml of acetonitrile. To the resultant solution were added 1 g of Gly(OEt) \cdot HCl, and then gradually 0.93 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.82 g of $C_{12}\text{-Ga-DP-diGly}$ (76). The yield was 100%.

20 Example 69

25 To 0.5 g of DCHA salt of $C_{12}\text{-Ga-DP}$ were added and dissolved 5 ml of chloroform and 2 ml of acetonitrile. To the resultant solution were added 5 g of Asp(OMe) \cdot HCl, and then gradually 0.35 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.44 g of $C_{12}\text{-Ga-DP-diAsp}$ (77). The yield was 97.1%.

Example 70

30 To 0.5 g of DCHA salt of $C_{12}\text{-Ga-DP}$ were added and dissolved 5 ml of chloroform and 2 ml of acetonitrile. To the resultant solution were added 0.75 g of Glu(OEt) \cdot HCl, and then gradually 0.44 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.46 g of $C_{12}\text{-Ga-DP-diGlu}$ (78). The yield was 99.4%.

35 Example 71

The procedure similar to those of Examples 17 and 62 was followed using 4.5 g of Ga-PP-Me and 45 ml of 10% HBr/HOAc, and 25 ml each of tetrahydrofurfuryl alcohol and tetrahydropyran-2-methanol instead of ethylene glycol to obtain 3.3 g of $_{H_4}\text{Fran-Ga-DP}$ (79) and 3.2 g of $_{H_4}\text{Pyran-Ga-DP}$ (81). The yields were 55.9% and 52.4% respectively.

45 Example 72

To 0.2 g of DCHA salt of (79) obtained in Example 71 were added and dissolved 4 ml of chloroform and 2 ml of acetonitrile. To the resultant solution were added 0.3 g of Asp(OMe) \cdot HCl, and then gradually 0.2 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 50 0.17 g of $_{H_4}\text{Fran-Ga-DP-diAsp}$ (80). The yield was 95.1%.

Example 73

55 To 0.3 g of DCHA salt of (81) obtained in Example 71 were added and dissolved 6 ml of chloroform and 3 ml of acetonitrile. To the resultant solution were added 0.4 g of Asp(OMe) \cdot HCl, and then gradually 0.3 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.25 g of $_{H_4}\text{Pyran-Ga-DP-diAsp}$ (82). The yield was 92.9%.

Example 74

To 0.3 g of DCHA salt of Mg-protoporphyrin were added and dissolved 20 ml of chloroform and 1 ml of pyridine. To the resultant solution were added 0.3 g of Tyr(OMe)^{*}HCl, and then gradually 0.3 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.1 g of Mg-PP-diTyr (88). The yield was 34.6%.

Example 75

The procedure similar to those of Examples 17 and 62 was followed using 3 g of PP-Me and 30 ml of 10% HBr/HOAc, and 18 ml each of ethylene glycol, octyl alcohol, decyl alcohol, undecyl alcohol, dodecyl alcohol, tetradecyl alcohol, hexadecyl alcohol and octadecyl alcohol separately to obtain 3.2 g, 1.78 g, 1.0 g, 0.89 g, 1.12 g, 0.75 g, 0.09 g, and 0.8 g of 2,4-bis[1-(2-hydroxyethoxyethyl)]deuteroporphyrin, 2,4-bis(1-octyloxyethyl)deuteroporphyrin, 2,4-bis(1-decyloxyethyl)deuteroporphyrin, 2,4-bis(1-undecyloxyethyl)-deuteroporphyrin, 2,4-bis(1-dodecyloxyethyl)-deuteroporphyrin, 2,4-bis(1-tetradecyloxyethyl)-deuteroporphyrin, 2,4-bis(1-hexadecyloxyethyl)-deuteroporphyrin, and 2,4-bis(1-octadecyloxyethyl)-deuteroporphyrin (hereinafter referred to as EG-DP, C₈-DP, C₁₀-DP, C₁₁-DP, C₁₂-DP, C₁₄-DP, C₁₆-DP, and C₁₈-DP respectively). The yields were respectively 88.9%, 42.6%, 22.4%, 19.1%, 23.6%, 14.9%, 1.7% and 14.3%.

20

Example 76

To 6 g of EG-DP obtained in Example 75 was added 1 liter of pyridine, and suspended with 40 g of magnesium perchlorate. The mixture was then reacted for 3.5 hours under heating (at 115 °C). After concentration, the reaction solution was added with water to precipitate crystals. The obtained precipitates were filtered off, dried and then hydrolyzed as in Example 8 to obtain 2.7 g of EG-Mg-DP (89). The yield was 43.5%.

30

Example 77

To 0.4 g of DCHA salt of (89) was added and dissolved 24 ml of tetrahydrofuran. To the resultant solution were added 0.4 g of Tyr(OMe)^{*}HCl, and then gradually 85 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.12 g of EG-Mg-DP-diTyr (90). The yield was 23.0%.

Example 78

40

To 20 ml of acetic acid were added 1 g of PP-Me, 1 g of manganese acetate and 1 g of sodium acetate, suspended, and then reacted for 20 minutes under heating (75 - 78 °C). After reaction (confirmed by TLC), the reaction solution was added with water to precipitate crystals. The obtained precipitates were filtered off, dried and then hydrolyzed as in Example 8 to obtain 0.74 g of Mn-protoporphyrin (hereinafter referred to as Mn-PP). The yield was 70.8%.

Example 79

50

To 0.8 g of DCHA salt of Mn-PP obtained in Example 78 were added and dissolved 40 ml of chloroform and 2 ml of pyridine. To the resultant solution were added 0.6 g of Tyr(OMe)^{*}HCl, and then gradually 0.6 g of WSC while stirring. The procedure similar to that of Example 23 was thereafter followed to obtain 0.1 g of Mn-PP-monoTyr(OMe) (methyl ester of 95). The yield was 20.6%.

65

Example 80

To esters obtained in Example 79 was added 0.1N NaOH, and the resultant substance was heated

slightly and hydrolized. After the completion of reaction (confirmed by TLC), the procedure similar to that of Example 8 was followed to obtain 0.09 g of Mn-PP-monoTyr (95). The yield was 91.6%.

5 Example 81

To 0.3 g of DCHA salt of Mn-PP were added and dissolved 20 ml of chloroform and 1 ml of pyridine. To the resultant solution were added 0.3 g of Tyr(OMe)^{*}HCl, and then gradually 0.3 g of WSC while stirring. The procedure similar to those of Examples 7 and 80 was thereafter followed to obtain 0.1 g of Mn-PP-diTyr (96). The yield was 37.3%.

Example 82

15 To 10 g each of 2-[1-(2-hydroxyethoxy)ethyl]-4-ethenyl-deuteroporphyrin (hereinafter referred to as monoEG-DP) and EG-DP were added and dissolved separately 60 ml of chloroform and 20 ml of methanol. To the resultant substances were respectively added 10.2 g of manganese acetate dissolved in 8 ml of methanol while stirring, heated and reacted at 70 - 75 °C. After reaction (confirmed by TLC), the reaction solution was concentrated under reduced pressure. The obtained concentrate was then washed with water, 20 filtered, and the filtrate was dried to obtain 2.2 g of monoEG-Mn-DP (97) and 2.35 g of EG-Mn-DP (103) respectively. The yields were 22.0% and 20.8%.

Example 83

25 To 4 g of DCHA salt of (97) were added and dissolved 120 ml of chloroform and 60 ml of acetonitrile. To the resultant solution were added 3 g of Gly(OEt)^{*}HCl, and then gradually 4 g of WSC while stirring. The reaction was carried out for 80 minutes. After reaction was completed (confirmed by TLC), the reaction solution was washed with water, extracted with 4% NaHCO₃ solution and divided. To the water layer was 30 added 10% citric acid solution to adjust pH to 5.5. Thus adjusted water layer was extracted with chloroform, and concentrated under reduced pressure to obtain ethyl ester of monoEG-Mn-DP-monoGly (98). On the other hand, the chloroform layer was also concentrated under reduced pressure to obtain ethyl ester of monoEG-Mn-DP-diGly (99). The procedure similar to Example 8 was followed to hydrolyze respective esters to obtain 1.2 g of monoEG-Mn-DP-monoGly (98) and 1.5 g of monoEG-Mn-DP-diGly (99). The yields were 35 45.1% and 52.6% respectively.

Example 84

40 To 5 g of DCHA salt of (97) were added and dissolved 50 ml of chloroform and 100 ml of acetonitrile. To the resultant solution were added 2.5 g of Asp(OMe)^{*}HCl, and then gradually 3.2 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 1.1 g of monoEG-Mn-DP-diAsp (100). The yield was 27.0%.

45
Example 85

To 3 g of DCHA salt of (97) were added and dissolved 90 ml of chloroform and 45 ml of acetonitrile. To the resultant solution were added 3 g of Phe(OMe)^{*}HCl, and then gradually 3 g of WSC while stirring. The 50 procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 2.61 g of monoEG-Mn-DP-diPhe (101). The yield was 100%.

Example 86

55 To 4 g of DCHA salt of (97) were added and dissolved 180 ml of chloroform and 60 ml of acetonitrile. To the resultant solution were added 4 g of Tyr(OMe)^{*}HCl, and then gradually 3.75 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 3.59 g of monoEG-

Mn-DP-diTyr (102). The yield was 100%.

Example 87

5 To 30 g of Mn-protoporphyrin dimethyl ester (hereinafter referred to as Mn-PP-Me) was added and dissolved 300 ml of 10% HBr/HOAc. After being left standing for 24 hours, the resultant solution was concentrated under reduced pressure, and the Br derivative obtained by concentration was added and dissolved with 150 ml of ethylene glycol, and left standing for another 24 hours. After the reaction was
10 completed (confirmed by TLC), the reaction product was washed with water, hydrolyzed and recrystallized (acetone-ethyl acetate) as in Example 8 to obtain 20 g of EG-Mn-DP (103). The yield was 58.0%.

Example 88

15 To 2 g of DCHA salt of (103) were added and dissolved 20 ml of chloroform and 40 ml of acetonitrile. To the resultant solution were added 1 g of Gly(OEt)^{*}HCl dissolved in 1 ml of DMF, and then gradually 8 ml of 5% WSC chloroform solution while stirring. The procedure similar to that of Example 23 was thereafter followed to obtain 0.13 g of EG-Mn-DP-monoGly (104). The yield was 8.3%.

20

Example 89

To 2 g of DCHA salt of (103) were added and dissolved 20 ml of chloroform and 40 ml of acetonitrile.
25 To the resultant solution were added 1 g of Asp(OMe)^{*}HCl dissolved in 1 ml of DMF, and then gradually 3 ml of 5% WSC chloroform solution while stirring. The procedure similar to that of Example 23 was thereafter followed to obtain 0.13 g of EG-Mn-DP-monoAsp (108). The yield was 8.9%.

30 **Example 90**

To 5 g each of C₈-DP, C₁₀-DP, C₁₁-DP, C₁₂-DP, C₁₄-DP, C₁₅-DP and C₁₈-DP were added separately and dissolved 30 ml of chloroform and 10 ml of methanol. To the resultant solutions were respectively added 5.1 g of manganese acetate dissolved in 4 ml of methanol, and the products were treated similarly
35 as in Example 82 and Mn ion complexed to obtain respectively 5.71 g, 4.75 g, 4.29 g, 4.56 g, 5.0 g, 5.1 g and 5.5 g of C₈-Mn-DP, C₁₀-Mn-DP, C₁₁-Mn-DP, C₁₂-Mn-DP, C₁₄-Mn-DP, C₁₅-Mn-DP and C₁₈-Mn-DP. The yields were respectively 84.3%, 66.4%, 58.4%, 60.5%, 63.1%, 61.4% and 63.4%.

40 **Example 91**

To 20 g of Mn-PP-Me was added and dissolved 200 ml of 10% HBr/HOAc. After being left standing for 24 hours, the resultant solution was concentrated under reduced pressure at 50 °C or below, and the obtained Br derivative was added and dissolved with 100 ml of octanol. The resultant solution was left
45 standing for 24 hours. After the reaction (confirmed by TLC), the reaction product was washed with water, hydrolyzed as in Example 8, and recrystallized (ethyl acetate - hexane) to obtain 15 g of C₈-Mn-DP. The yield was 55.1%.

50 **Example 92**

To 2 g of DCHA salt of C₈-Mn-DP obtained in Example 90 were added and dissolved 20 ml of chloroform and 40 ml of acetonitrile. To the resultant solution were added 1 g of Gly(OEt)^{*}HCl dissolved in 1 ml of DMF, and then gradually 2 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.4 g of C₈-Mn-DP-diGly (115). The yield was 25.0%.

Example 93

To 0.7 g of DCHA salt of C₈-Mn-DP were added and dissolved 14 ml of chloroform and 7 ml of methanol. To the resultant solution were added 0.93 g of Asp(OMe)^{*}HCl, and then gradually 1.1 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.53 g of C₈-Mn-DP-diAsp (116). The yield was 90.0%.

5

Example 94

To 0.5 g of DCHA salt of C₁₀-Mn-DP obtained in Example 90 were added and dissolved 11.4 ml of chloroform and 3.8 ml of acetonitrile. To the resultant solution were added 0.6 g of Gly(OEt)^{*}HCl, and then gradually 0.6 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.37 g of C₁₀-Mn-DP-diGly (117). The yield was 96.7%.

15 Example 95

To 0.9 g of DCHA salt of crude C₁₀-Mn-DP were added and dissolved 18 ml of chloroform and 8 ml of acetonitrile. To the resultant solution were added 1 g of Leu(OMe)^{*}HCl, and then gradually 1.7 g of WSC while stirring. The procedure similar to those of Examples 7, 8 and 54 was thereafter followed to obtain respectively 0.36 g and 0.01 g of C₁₀-Mn-DP-diLeu (119) and C_{10(mono)}-Mn-DP-diLeu (129). The yields were respectively 47.4% and 1.2%.

Example 96

25

To 0.5 g of DCHA salt of C₁₀-Mn-DP were added and dissolved 10 ml of chloroform and 5 ml of acetonitrile. To the resultant solution were added 0.3 g of Ser(OMe)^{*}HCl, and then gradually 10 ml of 5% WSC chloroform solution while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.34 g of C₁₀-Mn-DP-diSer (120). The yield was 84.9%.

30

Example 97

To 0.45 g of DCHA salt of C₁₀-Mn-DP were added and dissolved 5 ml of chloroform and 4 ml of acetonitrile. To the resultant solution were added 0.59 g of Asp(OMe)^{*}HCl, and then gradually 7 ml of 10% DCC chloroform solution while stirring. The procedure similar to those of Examples 7, 8 and 54 was thereafter followed to obtain 0.1 g of C₁₀-Mn-DP-diAsp (122). The yield was 26.2%.

40 Example 98

To 0.45 g of DCHA salt of C₁₀-Mn-DP were added and dissolved 9 ml of chloroform and 4 ml of acetonitrile. To the resultant solution were added 0.59 g of [D]Asp(OMe)^{*}HCl, and then gradually 0.7 g of WSC while cooling and stirring. The procedure similar to those of Examples 7, 8 and 54 was thereafter followed to obtain 0.15 g of C₁₀-Mn-DP-di[D]Asp (123). The yield was 39.4%.

Example 99

To 0.2 g of DCHA salt of crude C₁₀-Mn-DP were added and dissolved 4.5 ml of chloroform and 1.5 ml of acetonitrile. To the resultant solution were added 0.29 g of Glu(OEt)^{*}HCl, and then gradually 0.3 g of WSC while stirring. The procedure similar to those of Examples 7, 8 and 54 was thereafter followed to obtain respectively 0.06 g and 0.01 g of C₁₀-Mn-DP-diGlu (124) and C_{10(mono)}-Mn-DP-diGlu (130). The yields were respectively 34.6% and 7.8%.

55

Example 100

To 0.5 g of DCHA salt of C₁₀-Mn-DP were added and dissolved 12 ml of chloroform and 4 ml of acetonitrile. To the resultant solution were added 0.7 g of Phe(OMe)[•]HCl, and then gradually 0.75 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.44 g of C₁₀-Mn-DP-diPhe (125). The yield was 98.6%.

5

Example 101

To 0.13 g of DCHA salt of (117) obtained in Example 94 were added and dissolved 3 ml of chloroform and 1 ml of acetonitrile. To the resultant solution were added 0.12 g of Asp(OMe)[•]HCl, and then gradually 0.18 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.11 g of C₁₀-Mn-DP-diGly-diAsp (126). The yield was 93.2%.

15 Example 102

To 0.33 g of DCHA salt of (119) obtained in Example 95 were added and dissolved 4 ml of chloroform and 1.5 ml of acetonitrile. To the resultant solution were added 0.34 g of Asp(OMe)[•]HCl, and then gradually 0.33 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.24 g of C₁₀-Mn-DP-diLeu-diAsp (127). The yield was 79.5%.

Example 103

25 To 0.32 g of DCHA salt of (125) obtained in Example 100 were added and dissolved 7.5 ml of chloroform and 2.5 ml of acetonitrile. To the resultant solution were added 0.3 g of Asp(OMe)[•]HCl, and then gradually 0.25 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.23 g of C₁₀-Mn-DP-diPhe-diAsp (128). The yield was 78.3%.

30

Example 104

The procedure similar to those of Examples 17 and 62 was followed using 1 g of PP-Me and 10 ml of 10% HBr/HOAc, and 6 g each of geraniol, citronellol, dihydrocitronellol and menthol respectively instead of ethylene glycol to obtain 2,4-bis(1-geranyloxyethyl)-deuteroporphyrin, 2,4-bis(1-citronellyloxyethyl)-deuteroporphyrin, 2,4-bis(1-dihydrocitronellyloxyethyl)-deuteroporphyrin, and 2,4-bis(1-menthylloxyethyl)-deuteroporphyrin (hereinafter respectively referred to as C_{10(Gera)}-DP, C_{10(Citro)}-DP, C_{10(H₂Citro)}-DP and C_{10(Menthyl)}-DP). Each of the compounds obtained was treated similarly as in Example 90 and Mn ion complexed to respectively obtain 0.88 g, 0.4 g, 0.56 g and 0.08 g of C_{10(Gera)}-Mn-DP (131), C_{10(Citro)}-Mn-DP (133), C_{10(H₂Citro)}-Mn-DP (136), and C_{10(Menthyl)}-Mn-DP (139). The yields were respectively 49.3%, 22.6%, 31.5% and 4.5%.

Example 105

45

To 0.5 g of DCHA salt of (131) obtained in Example 104 were added and dissolved 10 ml of chloroform and 5 ml of acetonitrile. To the resultant solution were added 0.5 g of Asp(OMe)[•]HCl, and then gradually 0.4 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.4 g of C_{10(Gera)}-Mn-DP-diAsp (132). The yield was 95.2%.

50

Example 106

55 To 0.33 g of DCHA salt of crude mixture of (133) obtained in Example 104 were added and dissolved 6.6 ml of chloroform and 3.3 ml of acetonitrile. To the resultant solution were added 0.33 g of Asp(OMe)[•]HCl, and then gradually 0.27 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.27 g of Asp derivative mixture. The mixture was then passed through octylsilica (C8) high performance liquid chromatograph [eluent: MeOH-H₂O (19:1)], to obtain 0.04 g and

0.12 g of C_{10(Citro)}-Mn-monoAsp (134) and C_{10(Citro)}-Mn-diAsp (135) respectively. The yields were 15.8% and 42.9% respectively.

5 Example 107

To 0.66 g of DCHA salt of crude mixture of (136) obtained in Example 104 were added and dissolved 13.2 ml of chloroform and 6.6 ml of acetonitrile. To the resultant solution were added 0.66 g of Asp(OMe)-HCl, and then gradually 0.54 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.58 g of Asp derivative mixture. The mixture was then passed through octylsilica (C8) high performance liquid chromatograph [eluent: MeOH-H₂O (19:1)], to obtain 0.23 g and 0.04 g of C_{10(H₂Citro)}-Mn-diAsp (137) and C_{10(H₂Citro,mono)}-Mn-diAsp (138) respectively. The yields were 38.3% and 8.2% respectively.

15

Example 108

To 0.8 g of DCHA salt of crude C₁₂-Mn-DP obtained in Example 90 were added and dissolved 15 ml of chloroform and 5 ml of acetonitrile. To the resultant solution were added 0.8 g of Asp(OMe)-HCl, and then gradually 7 ml of 10% WSC chloroform solution while stirring. The procedure similar to those of Examples 7, 8 and 106 was thereafter followed to obtain 0.5 g and 0.15 g of C₁₂-Mn-DP-diAsp (143) and C_{12(mono)}-Mn-DP-diAsp (147) respectively. The yields were 73.1% and 25.8% respectively.

25

Example 109

To 0.18 g of DCHA salt of (143) obtained in Example 108 were added and dissolved 4.5 ml of chloroform and 1.5 ml of acetonitrile. To the resultant solution were added 0.36 g of Gly(OEt)-HCl, and then gradually 0.6 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.13 g of C₁₂-Mn-DP-diAsp-tetraGly (145). The yield was 96.5%.

Example 110

35 To 0.6 g of DCHA salt of C₁₄-Mn-DP obtained in Example 90 were added and dissolved 15 ml of chloroform and 5 ml of acetonitrile. To the resultant solution were added 2.25 g of Asp(OMe)-HCl, and then gradually 2 g of WSC dissolved in 7 ml of chloroform while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.5 g of C₁₄-Mn-DP-diAsp (149). The yield was 97.0%.

40

Example 111

The procedure similar to Examples 17 and 62 was followed using 5 g of PP-Me and 75 ml of 10% HBr/HOAc, and 30 ml each of farnesol, octadecenol, phytol, tetrahydrofurfuryl alcohol, tetrahydropyran-2-methanol, 3-pyridine-methanol and methionol respectively instead of ethylene glycol to obtain 2,4-bis(1-farnesyloxyethyl)-deuteroporphyrin, 2,4-bis(1-octadecenyoxyethyl)-deuteroporphyrin, 2,4-bis(1-phytyloxyethyl)-deuteroporphyrin, 2,4-bis(1-tetra-furfuryloxyethyl)-deuteroporphyrin, 2,4-bis[1-tetrahydro-2-pyran-methyloxy]ethyl]-deuteroporphyrin, 2,4-bis(1-nicotinyloxyethyl)-deuteroporphyrin and 2,4-bis[1-(2-methyl-thiopropoxy)ethyl]-deuteroporphyrin (hereinafter referred to as C_{15(farnesyloxyethyl)}-DP, C_{18(octadecenyoxyethyl)}-DP, C_{20(phytyloxyethyl)}-DP, H₄Fran-DP, H₄Pyran-DP, Nct-DP and Msp-DP respectively). Each of the compounds obtained was treated similarly as in Example 90 and Mn ion complexed to respectively obtain 3.52 g, 0.54 g, 0.3 g, 2.25 g, 2.84 g, 1.7 g and 1.58 g of C_{15(Farnesyloxyethyl)}-Mn-DP (151), C_{18(Octadecenyoxyethyl)}-Mn-DP (155), C_{20(Phytyloxyethyl)}-Mn-DP (158), H₄Fran-Mn-DP (159), H₄Pyran-Mn-DP (161), Nct-Mn-DP (163) and Msp-Mn-DP (165) respectively. The yields were 35.2%, 5.0%, 2.7%, 28.3%, 34.6%, 21.1% and 19.7% respectively.

55

Example 112

To 0.06 g of DCHA salt of C₁₆-Mn-DP obtained in Example 90 were added and dissolved 9 ml of chloroform and 3 ml of acetonitrile. To the resultant solution were added 0.5 g of Asp(OMe)^{*}HCl, and then gradually 0.6 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.01 g of C₁₆-Mn-DP-diAsp (153). The yield was 19.3%.

5

Example 113

To 0.84 g of DCHA salt of C₁₈-Mn-DP obtained in Example 90 were added and dissolved 20 ml of chloroform and 10 ml of acetonitrile. To the resultant solution were added 0.8 g of Asp(OMe)^{*}HCl, and then gradually 0.8 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.63 g of C₁₈-Mn-DP-diAsp. The yield was 86.3%.

To 0.78 g of DCHA salt of C₁₈-Mn-DP-diAsp obtained were added and dissolved 12.4 ml of chloroform and 6.2 ml of acetonitrile. To the resultant solution were added 1 g of Asp(OMe)^{*}HCl, and then gradually 1 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.43 g of C₁₈-Mn-DP-diAsp-tetraAsp (154). The yield was 44.5%.

Example 114

To 0.52 g of DCHA salt of (155) obtained in Example 111 were added and dissolved 10.4 ml of chloroform and 5.2 ml of acetonitrile. To the resultant solution were added 0.52 g of Asp(OMe)^{*}HCl, and then gradually 0.6 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.43 g of C₁₈(Oleyl)-Mn-DP-diAsp (156). The yield was 95.2%.

25

Example 115

To 0.32 g of DCHA salt of (159) obtained in Example 111 were added and dissolved 6.6 ml of chloroform and 3.3 ml of acetonitrile. To the resultant solution were added 0.33 g of Asp(OMe)^{*}HCl, and then gradually 0.27 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.28 g of H₄Fran-Mn-DP-diAsp (160). The yield was 98.4%.

35 Example 116

To 0.3 g of DCHA salt of (161) obtained in Example 111 were added and dissolved 6 ml of chloroform and 3 ml of acetonitrile. To the resultant solution were added 0.3 g of Asp(OMe)^{*}HCl, and then gradually 0.25 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.24 g of H₄Pyran-Mn-DP-diAsp (162). The yield was 83.0%.

Example 117

45 To 0.32 g of DCHA salt of (163) obtained in Example 111 were added and dissolved 6.6 ml of chloroform and 3.3 ml of acetonitrile. To the resultant solution were added 0.33 g of Asp(OMe)^{*}HCl, and then gradually 0.27 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.17 g of Nct-Mn-DP-diAsp (164). The yield was 63.5%.

50

Example 118

To 0.52 g of DCHA salt of (165) obtained in Example 111 were added and dissolved 10.4 ml of chloroform and 5.2 ml of acetonitrile. To the resultant solution were added 0.52 g of Asp(OMe)^{*}HCl, and then gradually 0.6 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.4 g of Msp-Mn-DP-diAsp (166). The yield was 92.0%.

Example 119

The procedure similar to those of Examples 17 and 62 was followed using 5 g of PP-Me and 75 ml of 10% HBr/HOAc, and 25 ml of octafluoropentyl alcohol instead of ethylene glycol to obtain 1.6 g of 2,4-bis(1-octafluoropentyloxyethyl)-deuteroporphyrin (hereinafter referred to as $C_5(F_{16})$ -DP). The resultant compound was treated similarly as in Example 90 and Mn ion complexed to obtain 1.68 g of $C_5(F_{16})$ -Mn-DP (167). The yield was 16.7%.

10 Example 120

To 0.3 g of DCHA salt of crude mixture of (167) obtained in Example 119 were added and dissolved 6 ml of chloroform and 3 ml of acetonitrile. To the resultant solution were added 0.3 g of Gly(OEt) \cdot HCl, and then gradually 0.3 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.27 g of Gly derivative mixture. The mixture was then passed through octylsilica (C8) high performance liquid chromatograph [eluent: MeOH-H₂O (3:1)], to obtain 0.08 g and 0.04 g of $C_5(F_{16})$ -Mn-DP-diGly (168) and $C_5(F_8)$ -Mn-DP-diGly (169) respectively. The yields were 33.8% and 20.9% respectively.

20 Example 121

To 0.3 g of DCHA salt of crude mixture of (167) obtained in Example 119 were added and dissolved 6 ml of chloroform and 3 ml of acetonitrile. To the resultant solution were added 0.3 g of Asp(OMe) \cdot HCl, and then gradually 0.3 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.33 g of Asp derivative mixture. The mixture was then passed through octylsilica (C8) high performance liquid chromatograph [eluent: MeOH-H₂O (3:1)], to obtain 0.1 g and 0.03 g of $C_5(F_{16})$ -Mn-DP-diAsp (170) and $C_5(F_8)$ -Mn-DP-diAsp (171) respectively. The yields were 38.6% and 14.0% respectively.

30

Example 122

To 0.38 g of DCHA salt of crude mixture of C_{12} -Mn-DP obtained in Example 90 were added and dissolved 9 ml of chloroform and 3 ml of acetonitrile. To the resultant solution were added 0.21 g of p-trifluoromethylphenylalanine methyl ester hydrochloride (hereinafter referred to as Phe(F_3)(OMe) \cdot HCl), and then gradually 0.75 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain Phe(F_6) derivative mixture. The resultant mixture was passed through octylsilica (C8) high performance liquid chromatograph [eluent: MeOH-H₂O (99:1)], to obtain 0.12 g and 0.01 g of C_{12} -Mn-DP-diPhe(F_6) (173) and $C_{12(mono)}$ -Mn-DP-diPhe(F_6) (175) respectively. The yields were 41.5% and 3.0% respectively.

Example 123

45

To 0.09 g of DCHA salt of (173) obtained in Example 122 were added and dissolved 2.4 ml of chloroform and 0.8 ml of acetonitrile. To the resultant solution were added 0.12 g of Glu(OEt) \cdot HCl, and then gradually 0.26 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.07 g of C_{12} -Mn-DP-diPhe(F_6)-diGlu (174). The yield was 82.5%.

50

Example 124

To 0.5 g each of C₈-DP and C_{12} -DP obtained in Example 75 was separately added 10 ml of dimethylacetamide, and the resultant mixture was suspended with 1.6 g of ferric chloride 6H₂O, and reacted for 3 hours under heating (100 °C). The reaction solution was then concentrated, added with water, and crystals were precipitated. The obtained precipitates were then filtered off, dried and then treated similarly as in Examples 8 and 62 to obtain 0.4 g and 0.14 g of C₈-Fe-DP and C_{12} -Fe-DP respectively. The

yields were 72.2% and 25.6% respectively.

Example 125

5 To 0.25 g of DCHA salt of C₈-Fe-DP obtained in Example 124 were added and dissolved 5 ml of chloroform and 2.5 ml of acetonitrile. To the resultant solution were added 0.25 g of Asp(OMe)⁺HCl, and then gradually 0.25 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.22 g of C₈-Fe-DP-diAsp (181). The yield was 98.0%.

10

Example 126

15 To 0.12 g of DCHA salt of crude mixture of C₁₂-Fe-DP obtained in Example 124 were added and dissolved 4 ml of chloroform and 2 ml of acetonitrile. To the resultant solution were added 0.12 g of Asp(OMe)⁺HCl, and then gradually 0.27 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.09 g of Asp derivative mixture. The resultant mixture was then passed through octylsilica (C8) high performance liquid chromatograph [eluent: MeOH-H₂O (99:1)], to obtain 0.04 g and 0.005 g of C₁₂-Fe-diAsp (183) and C_{12(mono)}-Fe-diAsp (184) respectively. The yields were 20 respectively 36.7% and 5.6%.

Example 127

25 To 0.64 g each of C₁₀-DP and C₁₂-DP obtained in Example 75 were added and dissolved respectively 20 ml of chloroform and 10 ml of methanol. The resultant solutions were further added with 1.82 g of cobalt acetate dissolved in 10 ml of methanol and reacted. The reaction solutions were concentrated and added with water, and crystals were precipitated. The obtained precipitates were filtered off, dried and then treated similarly as in Examples 8 and 62 to obtain 0.6 g and 0.53 g of C₁₀-Co-DP and C₁₂-Co-DP respectively.

30 The yields were 82.9% and 77.9% respectively.

Example 128

35 To 0.3 g of DCHA salt of C₁₀-Co-DP obtained in Example 127 were added and dissolved 15 ml of chloroform and 5 ml of acetonitrile. To the resultant solution were added 0.3 g of Asp(OMe)⁺HCl, and then gradually 0.35 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.26 g of C₁₀-Co-DP-diAsp (185). The yield was 96.4%.

40

Example 129

45 To 0.43 g of DCHA salt of C₁₂-Co-DP obtained in Example 127 were added and dissolved 10 ml of chloroform and 5 ml of acetonitrile. To the resultant solution were added 0.43 g of Asp(OMe)⁺HCl, and then gradually 0.4 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.23 g of C₁₂-Co-DP-diAsp (186). The yield was 59.2%.

Example 130

50 To 0.3 g of C₁₂-DP obtained in Example 75 were added and dissolved 10 ml of chloroform and 5 ml of methanol. To the resultant solution was added 0.84 g of copper acetate and reacted. The reaction liquid was concentrated, added with water, and crystals were precipitated. The obtained precipitates were filtered off, dried and then treated similarly as in Examples 8 and 62 to obtain 0.31 g of C₁₂-Cu-DP. The yield was 55 97.0%.

Example 131

To 0.4 g of DCHA salt of C₁₂-Cu-DP obtained in Example 130 were added and dissolved 10 ml of chloroform and 3 ml of acetonitrile. To the resultant solution were added 0.4 g of Asp(OMe)^{*}HCl, and then gradually 0.4 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.3 g of C₁₂-Cu-DP-diAsp (191). The yield was 83.0%.

5

Example 132

To 0.5 g each of EG-DP and C₁₂-DP obtained in Example 75 were respectively added and dissolved 15 ml of chloroform and 2.5 ml of methanol. The resultant solutions were added with 2.2 ml of 5% zinc acetate methanol solution and reacted. The reaction liquids were concentrated and added with water, and crystals were precipitated. The obtained precipitates were filtered off, dried and then treated similarly as in Examples 8 and 62 to obtain 0.41 g and 0.5 g of EG-Zn-DP (193) and C₁₂-Zn-DP respectively. The yields were 74.5% and 93.7% respectively.

15

Example 133

To 0.5 g of DCHA salt of (193) obtained in Example 132 were added and dissolved 22 ml of chloroform and 8 ml of acetonitrile. To the resultant solution were added 0.5 g of Tyr(OMe)^{*}HCl, and then gradually 7 ml of 10% WSC chloroform solution while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.12 g of EG-Zn-DP-diTyr (194). The yield was 24.7%.

25 Example 134

To 0.25 g of DCHA salt of C₁₂-Zn-DP obtained in Example 132 were added and dissolved 5 ml of chloroform and 2.5 ml of acetonitrile. To the resultant solution were added 0.25 g of Asp(OMe)^{*}HCl, and then gradually 0.25 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.21 g of C₁₂-Zn-DP-diAsp (197). The yield was 92.9%.

Example 135

To 5 g of EG-DP obtained in Example 75 was added 100 ml of DMF. The resultant solution was suspended with 10 g of indium chloride, and reacted for 0.5 hour under heating (120 °C). The reaction liquid was concentrated and added with water, and crystals were precipitated. The obtained precipitates were filtered off, dried and then hydrolyzed similarly as in Example 8 to obtain 5.4 g EG-In-DP (199). The yield was 88.9%.

40

Example 136

To 0.5 g of DCHA salt of (199) obtained in Example 135 was added and dissolved 30 ml of chloroform. To the resultant solution were added 0.5 g of Tyr(OMe)^{*}HCl, and then gradually 0.6 g of WSC while stirring. The procedure similar to those of Examples 7 and 8 was thereafter followed to obtain 0.12 g of EG-In-DP-diTyr (200). The yield was 24.6%.

The porphyrin derivatives according to the present invention have the properties to accumulate in tumor cells, to react to external energy, and to destroy tumor cells. Since they do not manifest toxicity in normal cells, they are most useful as a therapeutic agent or a diagnostic agent for cancer.

Fig. 1 is a photograph showing hemorrhagic necrosis of a cancer mass at 24 hours after administration of C_n-Ga-DP-diAsp (n = odd numbers, 44, 49, 53, 55 and 66), and

Fig. 2 is also a photograph showing hemorrhagic necrosis of a cancer mass at 24 hours after administration of C_n-Ga-DP-diAsp (n = even numbers, 48, 51, 54, 58, 68 and 77).

Fig. 3 is also a photograph showing hemorrhagic necrosis of cancer masses at 24 hours after administration of C₁₀-Mn-DP-PheAsp (128) on the right, C_{10(Gara)}-Mn-DP-diAsp (132) at the center, and C₈-Fe-DP-diAsp (181) on the left.

Fig. 4 is a photograph showing necrotic tumor cells of the group administered C₁₂-Mn-DP-diAsp

(143).

Fig. 5 is a photograph of tumor cells of the control group.

Fig. 6 is a graph showing tumor cell growth curves after administrations of the following substances.

○ : Control group

5 ● : C₁₀-Mn-DP-diAsp (122)■ : C₁₂-Mn-DP-diAsp (143)

Fig. 7 is a graph showing cell growth inhibitions after administrations of the following substances.

▲ : C₈-Ga-DP-diAsp (58) without irradiation△ : C₈-Ga-DP-diAsp (58) with irradiation10 ● : C₁₀-Mn-Dp-diAsp (122) without irradiation○ : C₁₀-Mn-DP-diAsp (122) with irradiation

■ : Photofrin II without irradiation

□ : Photofrin II with irradiation

15 Fig. 8 is a photograph showing an animal given Yag laser irradiation at 24 hours following administration of C₈-Ga-DP-diAsp (54).

Fig. 9 is a photograph showing an animal of the control group given Yag laser irradiation.

Fig. 10 through 19 are graphs showing mass spectra (SIMS-NOBA); Fig. 10 of methyl ester of EG-Ga-DP-monoSer (19), Fig. 11 EG-Ga-DP-monoAsp (22), Fig. 12 methyl ester of C₈-Ga-DP-diSer (57), Fig. 13 methyl ester of C₈-Ga-DP-diAsp (58), Fig. 14 (58), Fig. 15 methyl ester of C₈(mono)-Ga-DP-diAsp (62),20 Fig. 16 C₈-Mn-DP-diAsp (116), Fig. 17 C₁₀-Mn-DP-diAsp (122), Fig. 18 C₈-Ga-DP, and Fig. 19 ethyl ester of monoEG-Cu-DP-diGly. Figs. 20 through 24 are graphs showing NMR spectra (¹H-NMR); Fig. 20 C₄-Ga-DP-diAsp (51), Fig. 21 C₆-Ga-DP-diAsp (54), Fig. 22 C₈-Ga-DP-diAsp (58), Fig. 23 C₁₀(H₂Citro)-Ga-DP-diAsp (74), and Fig. 24 H₄Fran-Ga-DP-diAsp (80).

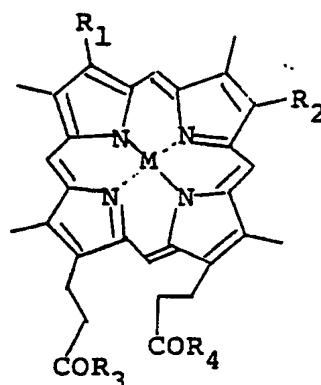
25

Claims

1. Metalloporphyrin compounds represented by the general formula (I)

30

35



40

45

wherein

R₁ and R₂ are each -CH=CH₂, -CH(OR)CH₃ or -CH(O-lower alkylene-OR)CH₃;R₃ and R₄ are -OH or a residue obtained by removing a hydrogen atom from a polyfunctional compound;

50 R is -H, alkyl, alkenyl, perfluoroalkyl, a cyclic compound, or a residue obtained by removing a hydrogen atom from a polyfunctional compound; and

M is a metal.

2. A metalloporphyrin compound of the general formula (I) according to claim 1 for use as a therapeutic or diagnostic agent for malignant tumors, as a tumor marker or as an agent for use in the missile therapy of cancers.

55



Fig. 1

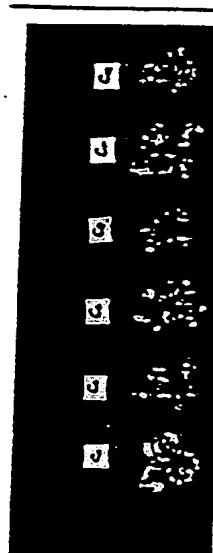
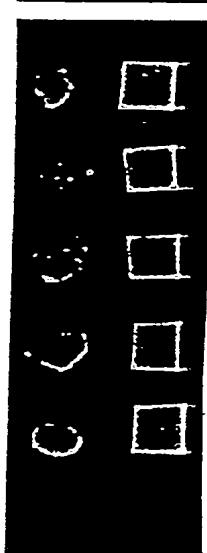


Fig. 4



Fig. 3

Fig. 5

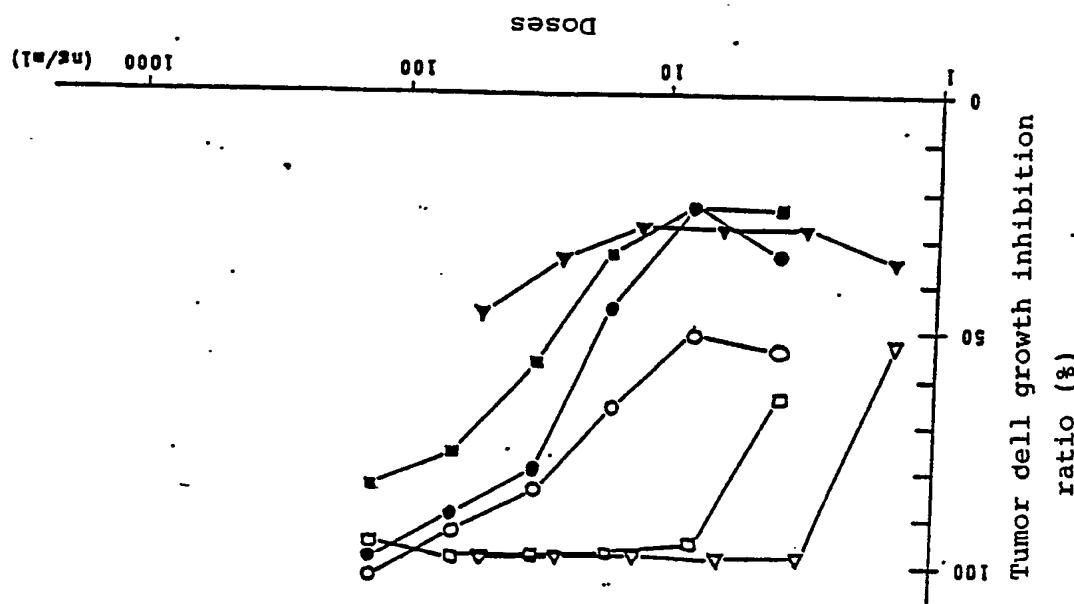


Fig. 7

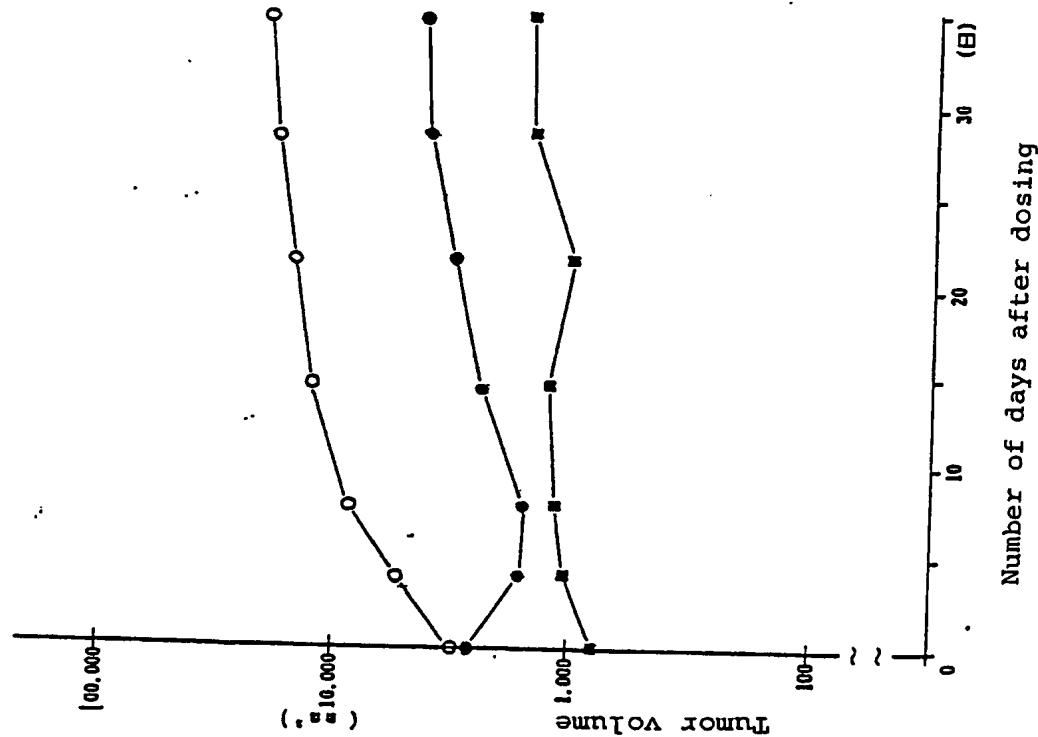


Fig. 6

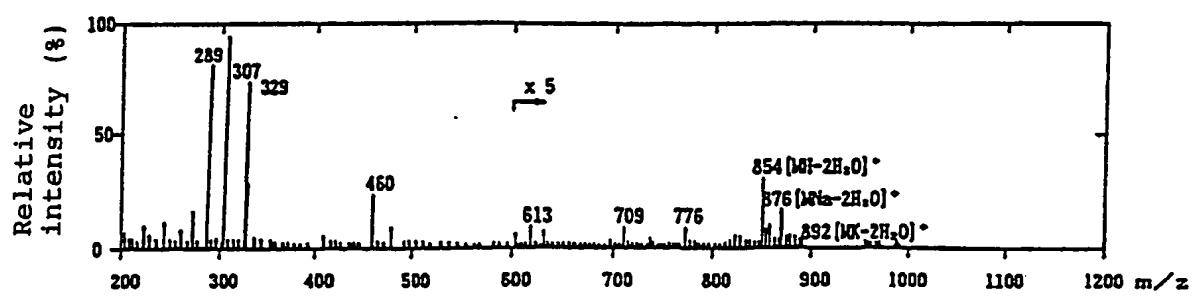


Fig. 10

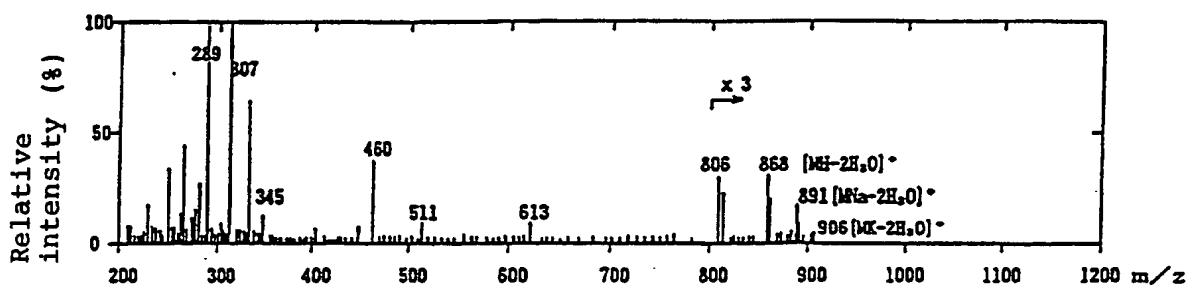


Fig. 11



Fig. 8 r



Fig. 9

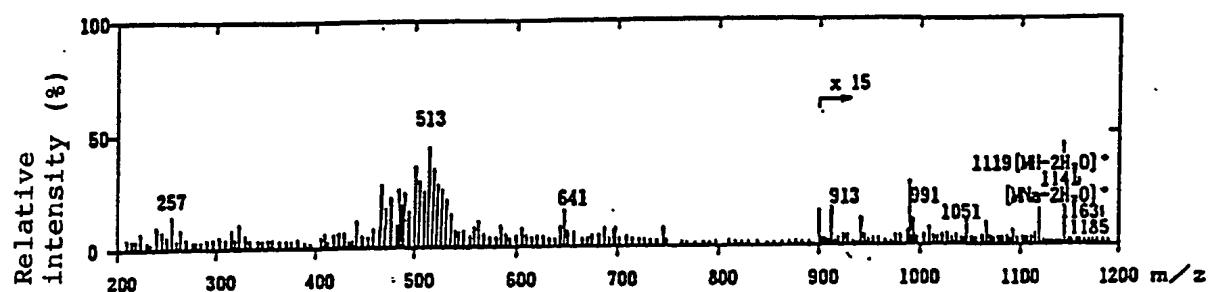


Fig. 14

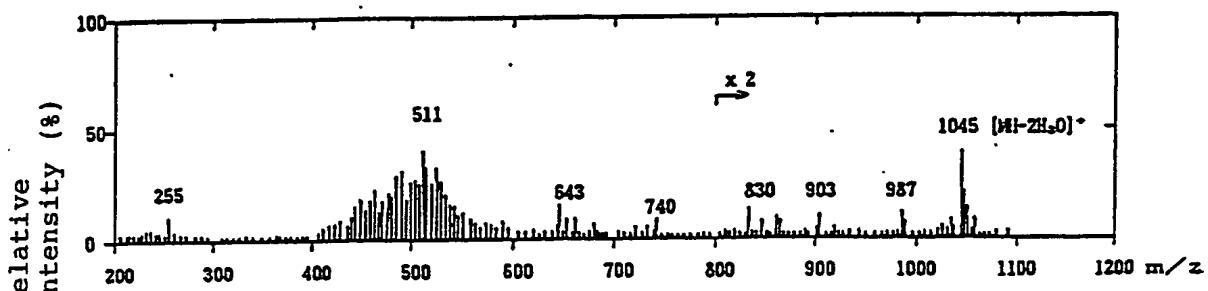


Fig. 15

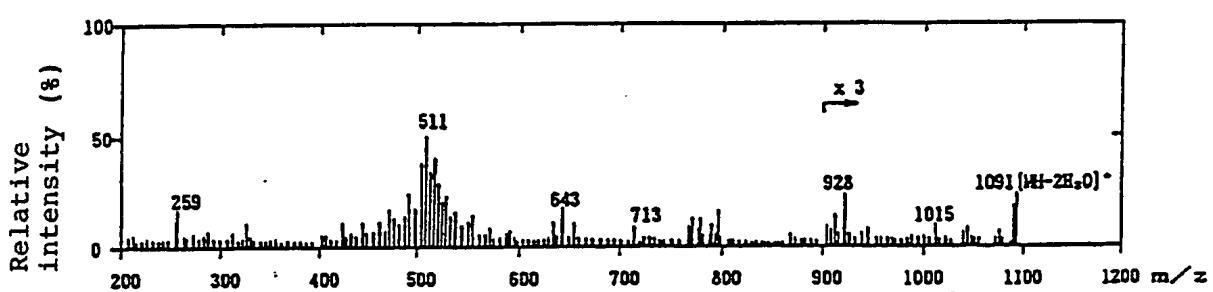


Fig. 12

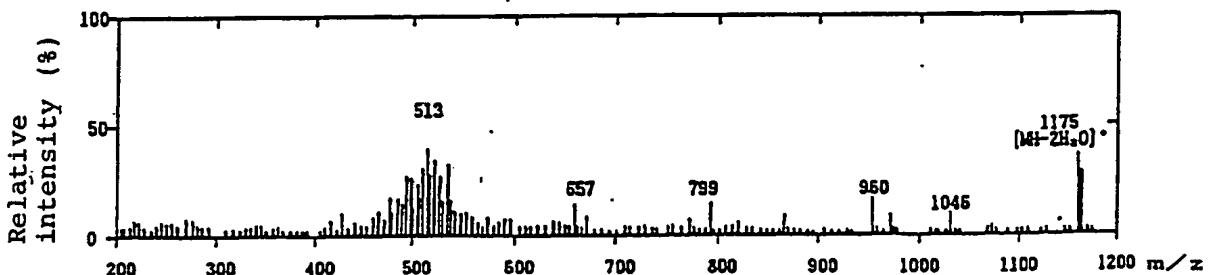


Fig. 13

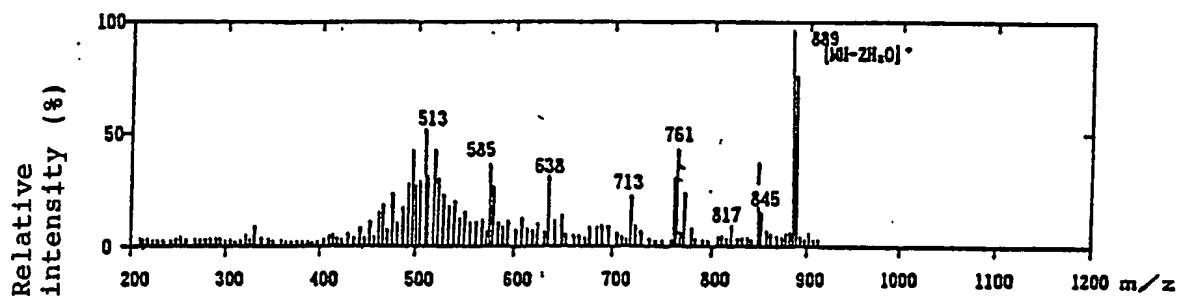


Fig. 18

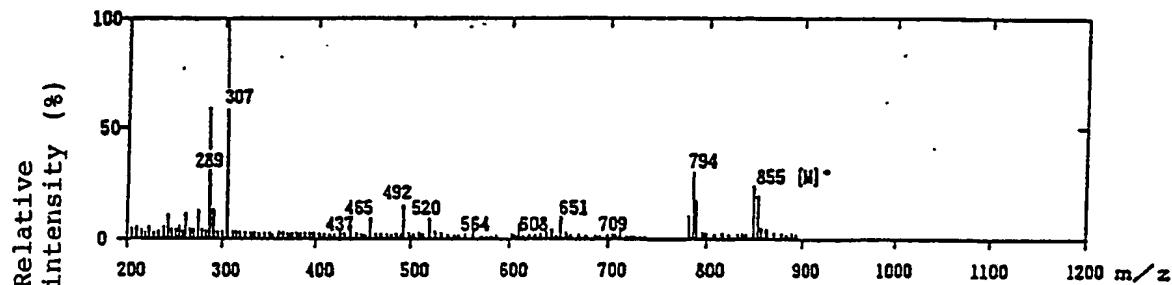


Fig. 19

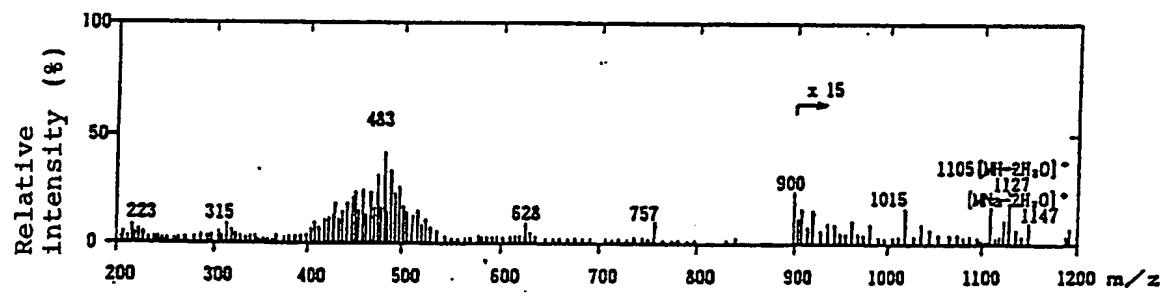


Fig. 16

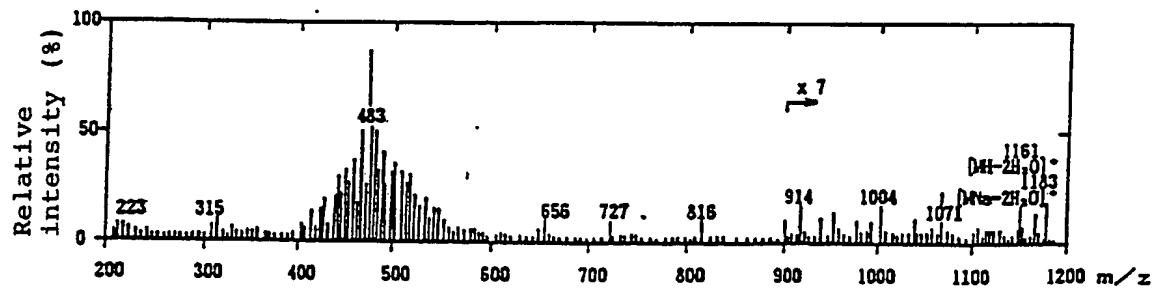


Fig. 17

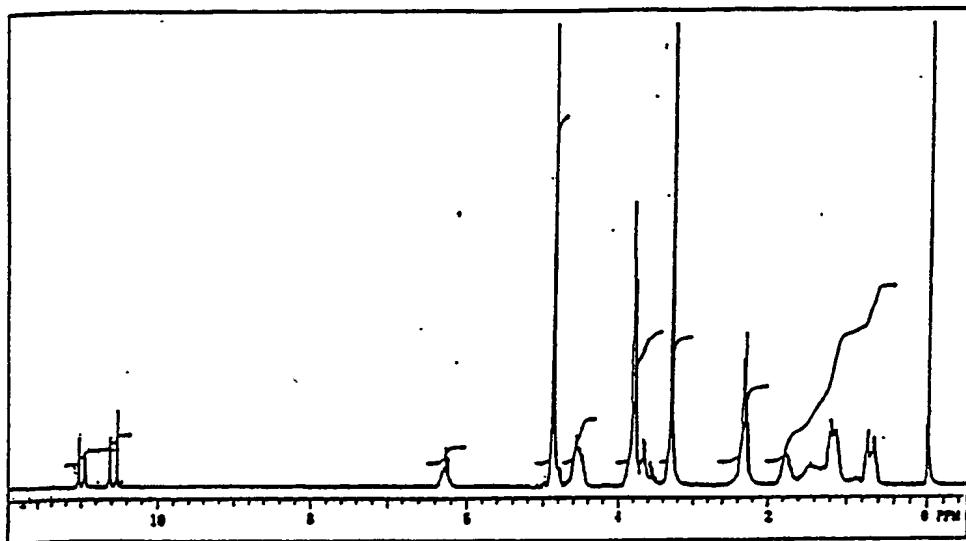


Fig. 21

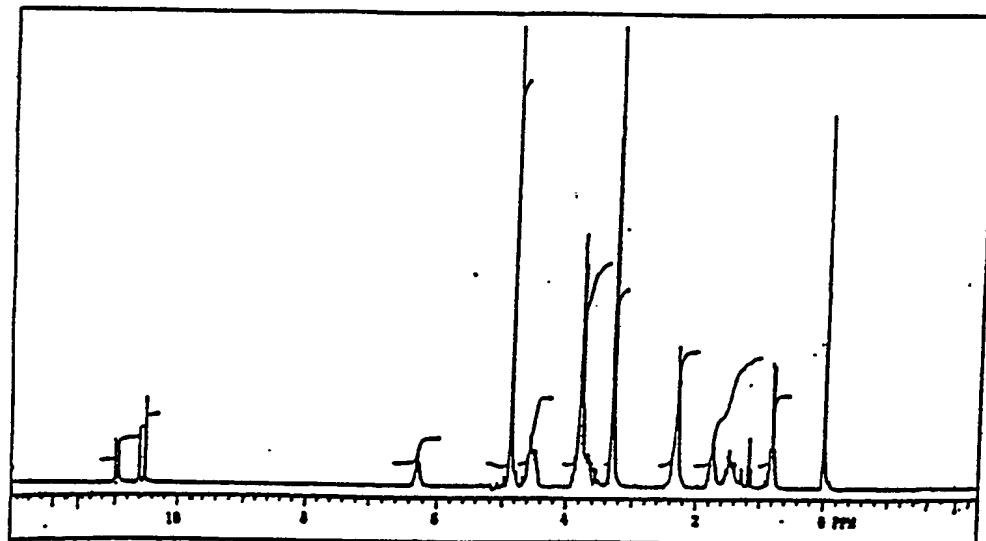


Fig. 20

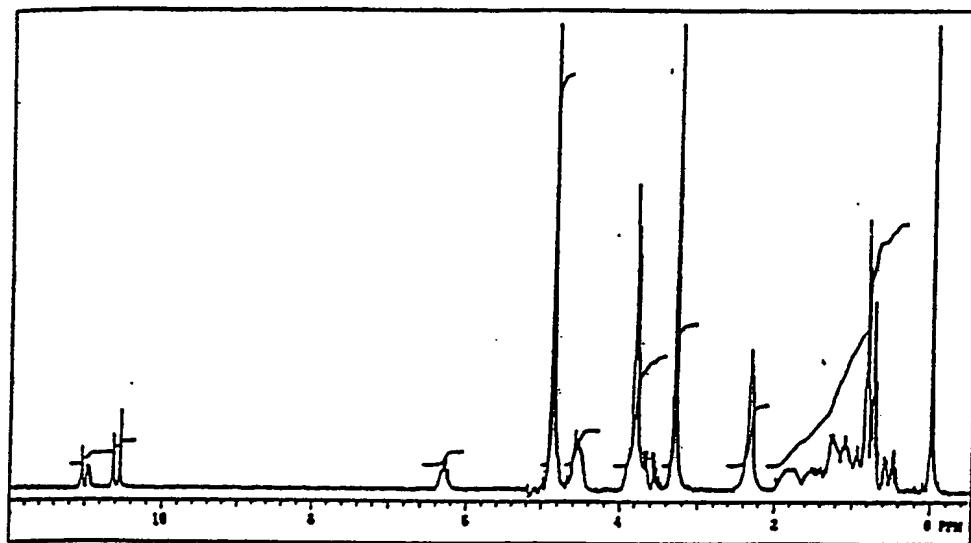


Fig. 23

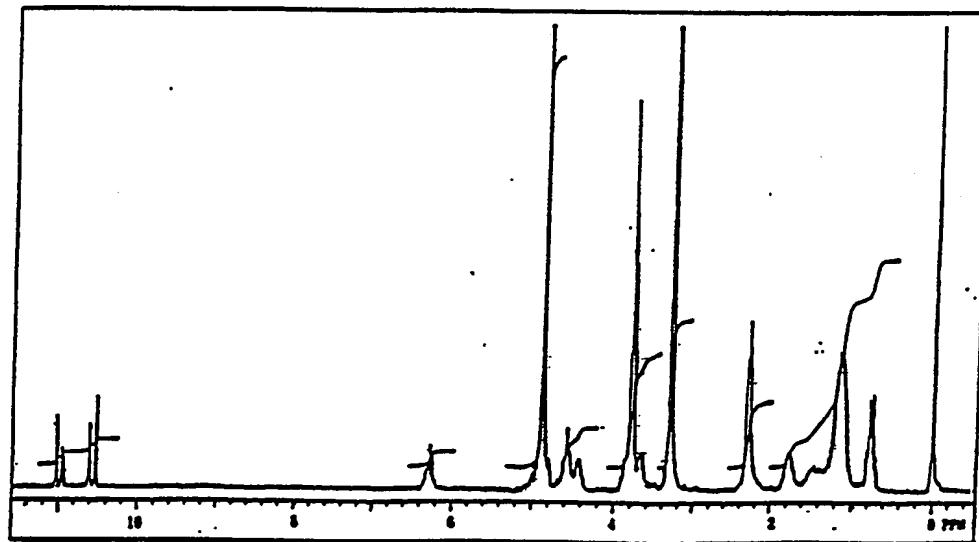


Fig. 22

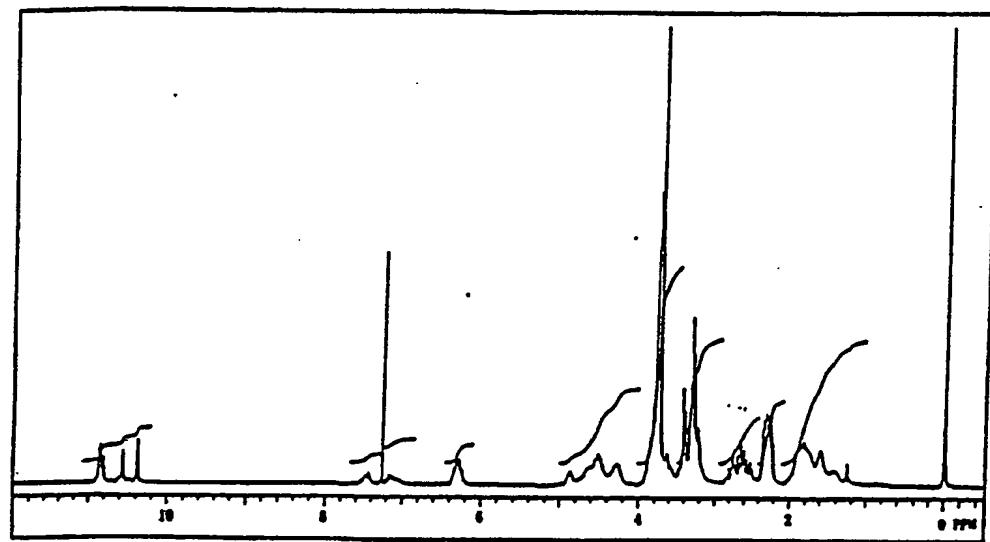


Fig. 24

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.